Monitoring Nociceptive Neuroplasticity

Quantitative Sensory Testing:
A Better Therapeutic Endpoint for Managing the Pain of Surgery?

Oliver H.G. Wilder-Smith

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To Elly

Pain is God's megaphone to a deaf world

- C.S. Lewis, The Problem of Pain

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I

INTRODUCTION

1. FOREWORD AND USER'S GUIDE

There is now a large body of evidence available to link nociception with subsequent alterations in nervous system function, both peripheral and central (1,2). In various animal models, studies have not only proven the existence of this link, but they have also provided a large amount of detail on the nature of and the mechanisms underlying these changes (3). Such nociceptive neuroplasticity, particularly that of central nervous system processing, is presently considered to be an important factor in the aetiology of pain after nociception, and has been suggested to play a significant role in subsequent acute and chronic pain outcomes (1,3,4). It should be noted at this point that in this book we will use the term neuroplasticity in the *broad* sense, and that it thus includes *both* functional and structural changes in nervous system function.

A large variety of animal models, both non-intact and intact, have been developed to provide valuable information on the mechanisms underlying pain and nociception (5-7). In this context, the most frequently studied species are rodents, particularly rats. Non-intact models are frequently either decerebrate or spinalised and are most useful for studying specific aspects of nociception. They may include neuroelectrophysiological elements such as single-neurone electrode recordings as well as various histobiochemical and similar techniques to understand biochemical and biomolecular aspects of the nociceptive process. This type of model also includes those with specific lesions in the central nervous system in order to better understand the pathways involved in pain and nociception processing. Intact models provide valuable information on the holistic, integrated response to nociception. In addition to electrophysiological and histobiochemical information of the type also obtained in non-intact models, intact models permit the observation of behavioural responses, which are regarded by some as providing surrogate models for human pain behaviour and experience. Intact animal models have also proven invaluable in the study of pathological pain states. Here, a disease state similar to a painful human disease state is induced, and thus mechanisms as well as effects of therapeutic interventions can be studied. Examples of such models include experimental monoarthritis, colitis or neuropathy, induced by the introduction of irritant material into (or near) joint, colon or large peripheral nerve. Several animal models of surgical pain, e.g. by incision (8), have now also been developed.

In animal models, the pattern of neuroplasticity following nociception is complex, varying with regard to time (e.g. acute vs. chronic), anatomical location (e.g. spinal vs. supraspinal systems), and nature (e.g. excitation vs. inhibition) (1,3,9,10). In the context of basic animal research, a considerable, albeit still far from complete, understanding of the biomolecular mechanisms involved in the response to nociception has been achieved (e.g. 1,3,11). In the animal model, it is now proving increasingly possible to link this understanding of nociceptive biomolecular mechanisms to our higher-order understanding of the neurophysiological changes accompanying nociception (i.e. nociceptive neuroplasticity). This linkage has been the basis of most of the pharmacological research in the field of pain of the

last 10-15 years, as it provides the connection between biomolecular mechanisms amenable to pharmacological modulation and neurophysiological changes considered relevant to the clinical phenomenon of pain (1,3,4). Thus the discovery and exploration of post-nociceptive neuroplasticity has provided - at least theoretically - the basis for a rational, mechanism-based approach to pain therapeutics and management (12-14).

The practical application of this discovery to clinical pain practice is desirable because the present symptom-based approach to pain treatment has clearly reached its limits, as illustrated by the significant numbers of pain patients, both chronic and acute, still not achieving satisfactory analgesia (15-18). The transfer of mechanism-based management - based on animal model results - to clinical practice has, however, proven difficult. This is demonstrated by the discussion surrounding one of the better-known postulates to result from the concept of nociceptive neuroplasticity, namely the postulate of pre-emptive analgesia for pain after surgery (1,4,12,13). One reason for this apparent transfer failure from basic to clinical science is surely the inherent difficulty of extrapolating from experimental animal data to the human clinical situation. A much more fundamental reason is likely to be the - generally unstudied and unproven - assumption that the nociceptive neuroplasticity demonstrated in animal studies can be equated with (or even reflected by) the subjective pain experience of a human patient as measured by pain scores or analgesic consumption (5,13). Both of these reasons make the collection - in the research and clinical setting - of direct measures of neuroplasticity *in the human* necessary and unavoidable as the basis for a transfer to clinical mechanism-based pain management.

In the context of human surgery, data as to the nature and course of neuroplasticity after surgical nociception remain sparse. Little is known about the relationship between measures of neuroplasticity (e.g. psychophysical measures) and measures of the patient's pain experience (e.g. pain scores, analgesic use), and the effects of clinically typical and relevant factors such as analgesia or pre-existing pain on nociceptive neuroplasticity are largely uninvestigated. The aim of this work is thus to provide a first basis for a transfer from symptom-orientated to mechanism-based pain management by validating the use of nociceptive neuroplasticity as an objective, clinically usable endpoint in the context of surgical pain and nociception.

The current work will address this aim in a number of ways. Firstly, we will present an integrated review of the theoretical background, particularly of knowledge from basic animal research, on nociception, biomolecular mechanisms, neuroplasticity and pain, with special emphasis on linking these phenomena. Secondly, based on our research, we will offer evidence validating neuroplasticity, as measured by quantitative sensory testing (QST), for quantifying both analgesia and nociception. Demonstrating that such QST use is feasible for clinical application will form a third thrust of the present work. Finally, we will provide an overview of the new information which application of QST-measured nociceptive neuroplasticity has brought in the context of our research. This overview will give insight into the real potential which nociceptive neuroplasticity has as a new, objec-

tive endpoint providing novel information unobtainable via current subjective measures, and thus for altering the way we practice perioperative pain and nociception management.

This book is structured as follows. The *background* section provides the theoretical (chapter 2) and practical (chapter 3) background to the topic under discussion, closing with an exposition of the overall goals of the research to be presented (chapter 4). In the subsequent two *studies* sections, we present our own research in this area. Each section contains an *introduction* to the topic which also includes a more detailed listing of the questions to be investigated by the research presented (chapters 5 and 9). The articles covering our research then follow. Each section is completed by a *summary* of the research presented (chapters 8 and 16), containing a specific listing of the answers to the questions posed in the introduction. Two published review articles (chapters 17 and 18) covering *controversies and clinical practice* in this field are presented in the next section. The final section presents an *overview discussion* (chapter 19) of the implications of our research for surgical pain management today together with an outlook for the future.

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II

BACKGROUND

2. THEORY - LINKING NOCICEPTION TO NEUROPLASTICITY

Two decades ago, the “classic” view of pain and nociception was still predominantly that of a hard-wired nervous system responding in a fixed way to various nociceptive inputs. Thus, noxious stimulation causes specific peripheral nociceptors to fire, with the signal then being passed on to the spinal cord by A-delta or C-fibre primary nociceptive afferent nerves. These fibres then terminate in a specific, highly spatially organised fashion in the spinal posterior horn, where they then synapse with second order neurons projecting up into the brain. After crossing the midline, these second order pain fibres enter the spinothalamic tract, located anterolaterally, traverse the brainstem in the lateral white funiculus and terminate - again in a highly somatotopically organised fashion - in the ventroposterolateral nucleus of the thalamus. Here, synaptic transmission again takes place onto third order nerve fibres, which then project on to sensory cortex, also in a somatotopically organised fashion. Since this time, it has become abundantly clear that pain processing and its pathologies cannot be explained within the context of a hard-wired neural processing system. What has emerged instead is the understanding that nociceptive input itself changes the way the pain and nociception-processing nervous system behaves and is wired. Thus nociceptive input alters the way the nervous system behaves at every level - peripheral, spinal and supraspinal - with quantity and quality of these changes depending not only on the quantity and quality of the nociceptive input but also on the vulnerability of the individual nervous system to such input.

Any discussion of the connection between nociceptive input (nociception) and resulting alterations to nervous system sensory processing (neuroplasticity) must cover both the neurophysiological changes taking place as well as the biomolecular mechanisms producing them. This then makes it possible to link particular effects on the nociceptive neuroplastic response with defined pharmacological interventions affecting nociceptive biomolecular mechanisms, thus providing the objective diagnostic process fundamental to the implementation of mechanism-based management strategies regarding nociception.

To prevent misunderstanding, we also need to briefly address the difference between nociception and pain. The pain experience by a person in response to a nociceptive input is multifactorial in origin, and nociception is thus accompanied by many other factors in finally determining the pain a patient subjectively experiences. However, all pain ultimately has its origin in some nociceptive event, and the modulation of nociception will always have an important - if not major - role to play in the management of pain, particularly if regarded over its entire time course. In addition, nociception is aetiologically much closer to the metabolic and immunological consequences of a noxious stimulus than pain is, making measures of nociceptive load much better candidates as surrogate disease outcome endpoints than measures of pain.

The aim of this chapter is thus to provide, based on animal studies over the last 10-15 years, an overview of the biomolecular mechanisms underlying the three main dimensions of the *integrated* neuroplastic response to nociception, namely its nature (i.e. excitatory vs. inhibitory), anatomical substrate (i.e. peripheral vs. spinal vs. supraspinal), and time course (i.e. acute vs. chronic). This will supply the theoretical grounding necessary to link nociception, biomolecular mechanisms and neuroplasticity, and hence justify the use of quantitative sensory testing for diagnosing nociceptive neuroplasticity as the foundation of a mechanism-based approach to nociception and pain therapeutics.

2.1. Excitatory Neuroplasticity

Excitatory changes in nervous system function after nociception occur in three phases. Already substantial and easily reversible, the first, acute phase (activation) takes place rapidly and manifests itself as a progressive increase in the neuronal response to repeated stimulation ("activation-dependent plasticity"). The second, sub-acute phase (modulation) develops - and is reversible - more slowly. Here neuronal excitability is increased due to altered transmembrane ionophore function subsequent to phosphorylation of receptors, ion channels and regulatory proteins ("sensitisation"). The changes in the third, chronic phase of neuroplasticity (modification) are long-lasting, take place much more slowly, and result in distinctly abnormal sensory processing, not only quantitatively but also qualitatively. They are the consequence of altered expression of neurotransmitters, receptors and ionophores with resulting disturbances in internal and external neuronal architecture and survival. It should be emphasised that the transitions between these three phases are fluid.

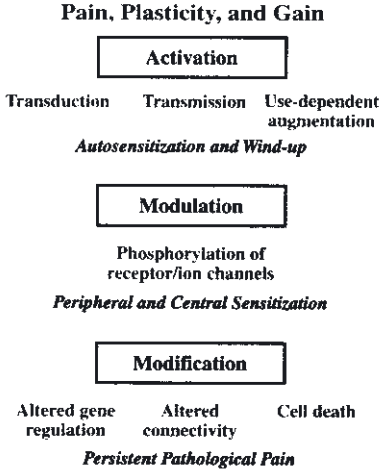


Figure 1: Summary of mechanisms of excitatory neuroplasticity and its time course (from reference 4).

2.1.1. Acute Excitatory Neuroplasticity: Activation

In the periphery, the initial effect of noxious stimulation is the activation of nociceptive transducers. These consist of receptor/ionophore complexes which depolarise (or reduce the resting potential of) the nociceptive nerve terminal in response to specific noxious stimuli of a chemical, thermal or mechanical nature (1-3). Activation of peripheral nociceptors can be elicited both by stimuli that do (autosensitisation) or do not (heterosensitisation) depolarise them, and results in a reduction of the high thresholds normally necessary to depolarise nociceptors (4). If the current resulting from transduction exceeds the membrane threshold value, an action potential follows, which is then conducted to the spinal cord via the primary afferent nociceptive nerve fibre.

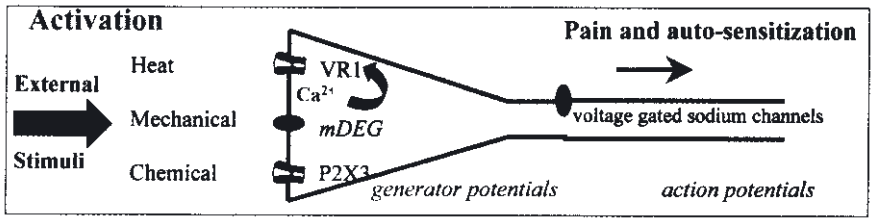
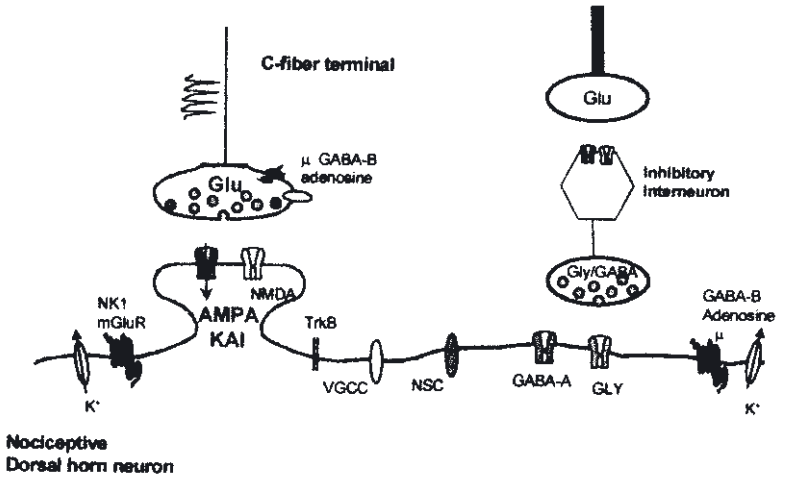
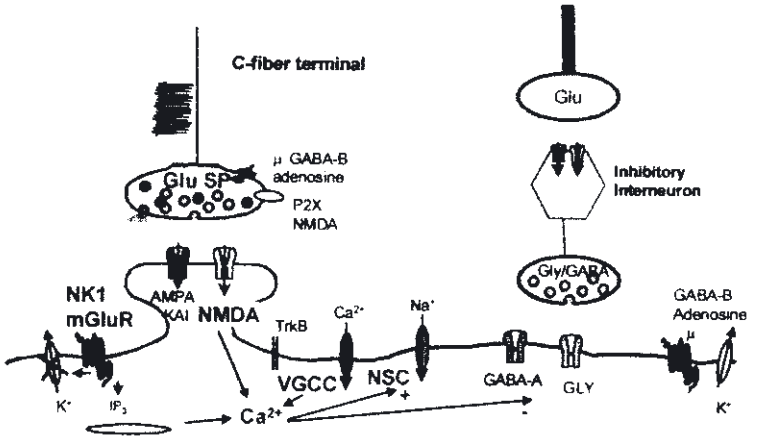


Figure 2: Summary of mechanisms of peripheral activation (from reference 4). Abbreviations: VR1 = vanilloid receptor; mDEG = proton gated degenerin Na+ ion channel; P2X3 = "fast" ATP-gated purinergic receptor.

At the spinal posterior horn, signals due to minor nociception (low intensity and frequency) are synaptically transmitted by the release of neurotransmitters, mainly acting via alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) and kainate receptors, with subsequent initiation of fast excitatory postsynaptic potentials (EPSPs) which encode stimulation onset, location, duration, and intensity (5). Activation-dependent plasticity (here termed wind-up) occurs with prolonged, higher frequency and intensity nociception via the generation of slow EPSPs (duration: tens of seconds), the consequence of N-methyl-D-aspartate (NMDA) receptor stimulation by glutamate as well as neuromodulator (e.g. substance P; acting via NK1 or mGluR receptors) co-release (6,7). Cumulative depolarisation, the result of temporal summation of slow EPSPs, is further enhanced with each successive input as calcium currents increase due to accompanying removal of Mg^{++} block of NMDA calcium ionophores and activation of voltage-gated non-selective cation channels (8-10). Thus generated action potentials are passed on for further processing to *supraspinal synaptic relays* (e.g. in the thalamus), believed to possess similar characteristics of activation as those described for the spinal posterior horn, although less investigated to date.



Activation :
AMPA/KAI receptor fast EPSPs



Activation :
Slow EPSPs, plateau potentials, summation & windup

Figure 3: Summary of fast and slow mechanisms of spinal activation (from reference 4). Abbreviations: ESPS = excitatory post-synaptic potential; Glu = glutamate; GABA = gamma-amino-butyric acid; AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid; NMDA = N-methyl-D-aspartate; KAI = kainate; NK1 = neurokinin 1; mGluR = metabotrophic glutamate receptor; TrkB = tyrosine receptor kinase B; VGCC = voltage-gated calcium channel; Gly = glycine; IP2 = inositol 4,5-bisphosphate; SP = substance P; P2X = ATP-gated purinergic receptor.

2.1.2. Sub-acute Excitatory Neuroplasticity: Modulation

Modulation resulting in increased excitability of neurones is considered to be the basis of the clinical phenomena of hyperalgesia (increased response to pain stimuli) and allodynia (normally non-painful stimuli result in pain) in the context of inflammatory or neuropathic pain (11). Modulation typically involves various intracellular kinase signalling cascades which phosphorylate and thus activate receptor/ionophore complexes and their regulatory proteins.

In the periphery, modulation of nociceptors (e.g. primary hyperalgesia) is mediated via sensitising substances released after tissue damage. These include inflammatory mediators, e.g. adenosine, adrenaline, bradykinin, prostaglandin or serotonin, as well as neurotrophic substances such as the various nerve growth factors (12,13). Peripheral modulation involves phosphorylation of the tetradotoxin resistant sensory neurone-specific sodium ion channel (SNS/PN3), and possibly the type 1 vanilloid receptor VR1, altering activation characteristics, increasing sodium current size with depolarisation, and leading to nociceptor hypersensitivity (14-16). Phosphorylation produces protein kinase A or C activation by intracellular kinases activated via receptors coupled to G protein- or membrane-bound tyrosine kinase (17-20).

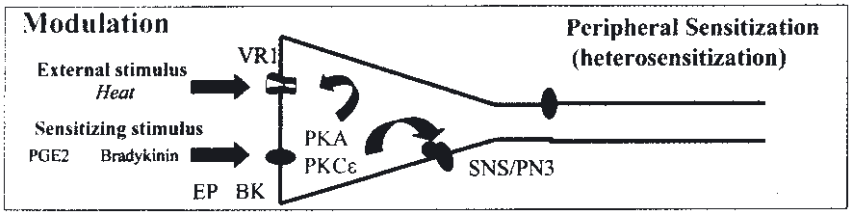


Figure 4: Summary of mechanisms of peripheral modulation (from reference 4). Abbreviations: EP = prostaglandin E receptor; BK = bradykinin; VR1 = vanilloid receptor; PKA = protein kinase A; PKC = protein kinase C; SNS/PN3 = tetradotoxin resistant sensory neurone-specific sodium ion channel.

Centrally, i.e. at spinal and supraspinal levels, modulation (central sensitisation) is evoked by primary afferent nociceptor input. Such input leads to facilitated excitatory synaptic and depressed inhibitory functions, affects activated (homosynaptic modulation) as well as adjacent (heterosynaptic modulation) synapses, and results in augmented responses and expanded receptive fields to nociceptive and non-nociceptive inputs (21-26). Homosynaptic modulation operates primarily via the AMPA receptor system and is dependent upon NMDA receptor activation and either high intensity or high frequency input, as seen in long-term potentiation of supraspinal (e.g. hippocampal) neurones (5,27). As nociceptors only fire at low frequencies, physiological homosynaptic modulation is likely to be limited to intense nociception. The mechanisms involved include

enhanced AMPA (and kainate) channel conductance and cell-surface expression as well as enhanced NMDA receptor function (5,27-29). In contrast, heterosynaptic modulation is elicited by low frequency input, being elicited by anything longer than transient C-fibre stimulation (30,31). It plays a major role at the spinal posterior horn, recruiting new input sources (e.g. from A-delta fibres), expanding receptive field size as well as facilitating synapses not previously activated by conditioning stimuli (32-34). Here, presynaptic release of neurotransmitters (NMDA) and neuromodulators (substance P, brain-derived neurotrophic factor BDNF) alters spinal posterior horn signal transduction via effects on postsynaptic ligand-gated ionophores (NMDA-R-glutamate), metabotropic receptors (mGluR-glutamate, NK1-substance P) and tyrosine kinase receptors (TrkB-BDNF), with important contributions from pre- and postsynaptically released prostaglandin E and prostacyclin acting on IP receptors (35,36). NMDA, NK1 and mGluR receptor activation plays a central and crucial role in the process of modulation and central sensitisation, with two main mechanisms being described for this increase in cell gain. The first operates via suppression of Mg^{++} block of NMDA channels, the result of cumulative depolarisation with summing of slow synaptic potentials, as described above (37). The second

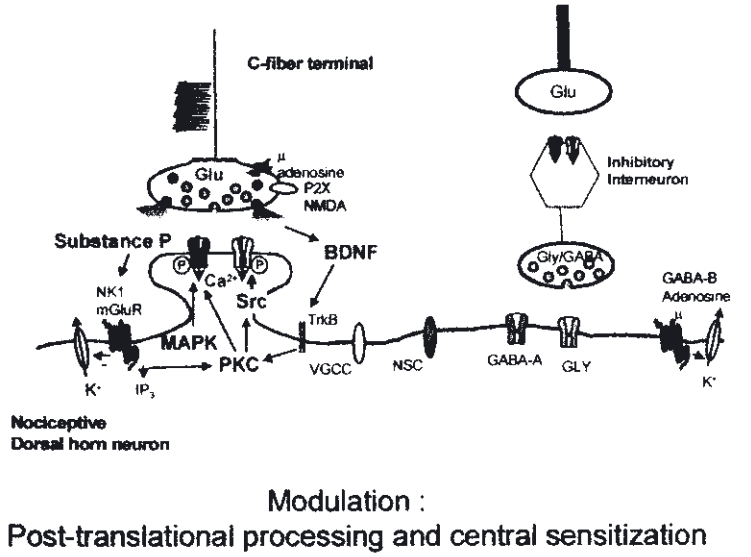


Figure 5: Summary of mechanisms of central modulation (from reference 4). Abbreviations: Glu = glutamate; P2X = ATP-gated purinergic receptor; NMDA = N-methyl D-aspartate; BDNF = brain-derived neurotrophic factor; NK1 = neurokinin 1; mGluR = metabotrophic glutamate receptor; IP3 = inositol 1,4,5-trisphosphate; MAPK = mitogen-activated protein kinase; PKC = protein kinase C; Src = a tyrosine kinase; TrkB = tyrosine receptor kinase B; VGCC = voltage-gated calcium channel; GABA = gamma-amino-butyric acid; GLY = glycine.

mechanism results in enhanced NMDA ionophore gating, e.g. via phosphorylation (35,36). This most likely occurs via several signalling cascades which increase intracellular Ca^{++} concentrations and activate calcium-dependent enzymes (protein kinase C, calmodulin kinase), protein kinase A (via G-protein coupled receptors, e.g. NK1, EP, mGluR) and/or tyrosine kinases (e.g. trkB receptor, itself a tyrosine kinase activating other tyrosine kinases such as Src or protein kinase C) (35,36,38). These mechanisms have also been demonstrated to be involved in excitatory amino acid receptor upregulation (non-receptor protein tyrosine kinase Src for NMDA receptors) or channel insertion (protein kinase C for AMPA receptors) (38,39). Other mechanisms independent of the NMDA receptor may, however, also play a role in central modulation, e.g. via altered expression of AMPA receptors, which permits increased neuronal Ca^{++} influx and thus long-lasting facilitation of synaptic transmission (28,29,40).

Two other aspects need to be considered regarding central modulation. First, it should be remembered that central modulation also involves depression of *inhibitory systems*. At the spinal level, e.g., activation of A-delta afferents can cause long-lasting depression of inhibitory, largely GABAergic and glycinergic, primary afferent synapses (4,41). Again, this effect is dependent upon NMDA receptor activation and subsequent rises in postsynaptic intracellular calcium concentrations. Second, *supraspinal systems* make a significant contribution to development and maintenance of central sensitisation (42). Such descending facilitatory systems frequently originate in the same brainstem regions as those producing descending inhibition (e.g. the rostral ventromedial medulla RVM) (42). It seems that low intensity electrical or chemical stimulation of these sites will tend to facilitate spinal nociception (e.g. via activation of “on-cells”, mainly found in the nucleus raphe of the RVM), while high intensity electrical or chemical stimulation will result in spinal inhibition (e.g. via activation of RVM “off-cells”) (43-46). However, the facilitatory and inhibitory systems operate via distinct anatomical spinal pathways (e.g. ventrolateral vs. dorsolateral funiculi) and receptor systems (e.g. serotoninergic and cholecystokininergic vs. cholinergic and monoaminergic receptors) (42). Regarding facilitation originating in the RVM, it is proposed that nociceptive input to the RVM via primary afferents and then spinobulbal tracts (and possibly direct hepatic vagal afferents and the nucleus tractus solitarius) activate RVM on-cells via mechanisms involving NMDA and neurotensin receptors as well as nitric oxide (43,45,47-49). These on-cells then project back to spinal posterior horn laminae I, II and V to produce facilitation of spinal nociceptive transmission (50,51). The important role of supraspinal facilitation in central modulation is supported by a number of studies demonstrating suppression of central sensitisation due to inflammation or nerve damage by spinal cord transection or inactivation of supraspinal sites (52-57).

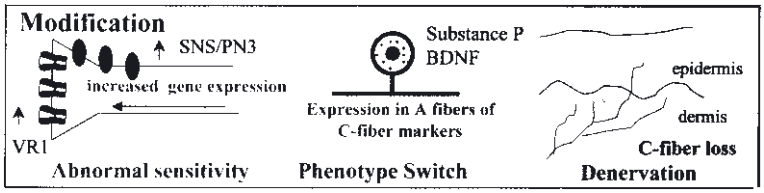


Figure 6: Summary of mechanisms of peripheral modification (from reference 4). Abbreviations: VR1 = vanilloid receptor; SNS/PN3 = tetradotoxin resistant sensory neurone-specific sodium ion channel; BDNF = brain-derived neurotrophic factor.

2.1.3. Chronic Excitatory Neuroplasticity: Modification

In peripheral modification, changes in target-derived growth factors in primary sensory neurones or peripheral nociceptors play a major role. These signal molecules, which normally undergo retrograde axonal transport from the periphery (target) to the centre (cell body), increase with inflammation and decrease with nerve (axon) damage due to loss of contact with the target (58). The function of target-derived growth factors changes in the course of development, being vital for neuronal survival early on, but then contributing to neuronal phenotype maintenance in the adult phase (4,58). Alterations in target-derived growth factor levels lead to significant changes in neuronal function via modified expression of ionophores, neurotransmitters, synaptic neuromodulators and G protein-linked receptors, as well as growth-associated and structural proteins (4,58). Another mechanism involved in peripheral modulation is change in sensory neurone transcription elicited via calcium influx through purely voltage-gated ionophores (36).

Inflammation is associated with an *increase* in target-derived growth factors. This causes upregulation of constitutive gene expression such as for SNS and VR1, making the peripheral terminal more prone to sensitisation, e.g. via inflammatory mediators (59,60). Such effects are supported by increased production of synaptic neuromodulators such as substance P or BDNF (61-63). Inflammation also results in induction of novel genes. An important example is the new expression of substance P and BDNF by A-delta fibres (and even sometimes A-beta fibres), which acquisition of the neurochemical features of C-fibres dramatically increases the ability of tactile stimulation of inflamed tissue to produce central sensitisation (36,64,65). In contrast, peripheral nerve injury results in a *decrease* of target-derived growth factors, and thus reduced levels of substance P, SNS, VR1 and CGRP. In addition, μ-opioid receptor expression is decreased, perhaps contributing to decreased opioid sensitivity, and brain sodium channel III production is increased, perhaps promoting increased ectopic neuronal activity (60,66-68). However, as in inflammation, BDNF production is increased in peripheral nerve injury, and similar

phenotype changes with expression of novel genes are observed, e.g. substance P and BDNF expression in A-delta fibres, permitting these to induce central sensitisation (69,70,71). Furthermore, nerve injury is associated with delayed sensory fibre loss, preferential for C-fibres, as well as spinal rewiring through A-beta fibres sprouting to establish functional synaptic contacts with regions normally only supplied by C-fibre input (i.e. superficial as opposed to deep posterior horn laminae) (72-75). The latter phenomenon is highly abnormal, likely contributing to the frequently observed, refractory tactile allodynia and other sensory pathologies seen in neuropathic pain syndromes.

Central modification (e.g. in posterior horn neurones), e.g. with inflammation or nerve injury, involves further modified transcription, with alterations in transmitters/modulators (dynorphin, enkephalin, GABA, COX2) and receptors (e.g. NK1, TrkB, GABA) subsequent to protein kinase cascade activation (e.g. mitogen-activated protein kinase, MAPK or cAMP responsive element-binding protein, pCREB) (76-78). These changes are probably due to increased electrical activity resulting in greater calcium influx via voltage-gated calcium channels (4). Again, inflammation is associated with *increased* expression of receptors and associated substances, generally the same ones as in peripheral modification, with similar but central effects producing increased central modulation (58).

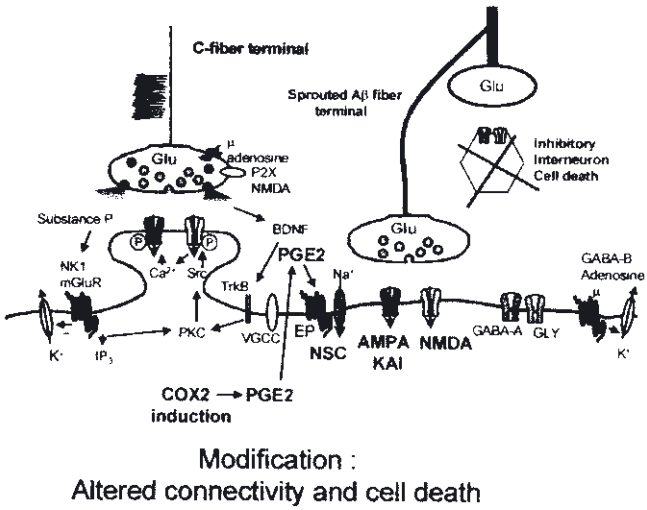


Figure 7: Summary of mechanisms of central modification (from reference 4). Abbreviations: Glu = glutamate; P2X = ATP-gated purinergic receptor; NMDA = N-methyl D-aspartate; BDNF = brain-derived neurotrophic factor; COX2 = cyclooxygenase 2; PGE2 = prostaglandin E2; NK1 = neurokinin 1; mGluR = metabotrophic glutamate receptor; IP3 = inositol 1,4,5-trisphosphate; PKC = protein kinase C; TrkB = tyrosine receptor kinase B; VGCC = voltage-gated calcium channel; EP = endoprostanoid; AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid; KAI = kainate; GABA = gamma-amino-butyric acid; GLY = glycine.

Nerve damage results in *decreased* inhibition, e.g. via reductions in receptors and neurotransmitters as well as loss of inhibitory interneurones (79,80). The latter process is initiated by neuronal injury discharge and ectopic activity, with subsequent cell death in the superficial spinal posterior horn laminae, where inhibitory interneurones are mainly localised (81,82).

2.2. Inhibitory Neuroplasticity

In intact organisms, nociceptive input elicits not only excitation but also inhibitory responses. Such an interaction of excitatory and inhibitory systems is typical for other sensory systems and for the central nervous system in general. Nociceptive processing is no exception in this respect, and inhibitory responses form part of the complex modulation which nociceptive signals undergo as they are transmitted from peripheral to central in the nervous system (83). Inhibitory neuroplasticity can be divided into two main types, spinal and supraspinal inhibition.

2.2.1 Spinal Inhibitory Neuroplasticity

Spinal inhibition is mainly triggered by innocuous stimuli transmitted via large diameter cutaneous afferents (e.g. A-beta fibres). This mechanism and its input is segmentally organised, being most effectively elicited by (non-noxious) mechanical stimulation in the

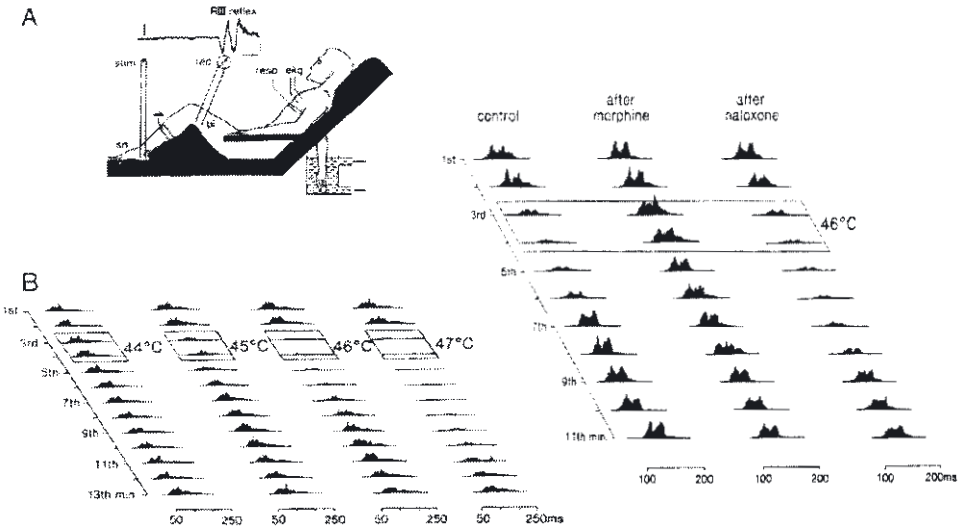


Figure 8: DNIC demonstrated in the human model (from reference 105). Left: Setup of model and increasing inhibitory effect of hotter conditioning stimulus. Right: Inhibitory effect of morphine on DNIC and its reversal by naloxone.

inhibitory receptive fields surrounding the excitatory receptive fields (e.g. secondary hyperalgesia) of convergent neurones (83,84). Propriospinal controls, possibly involving an upper cervical relay, and triggered by noxious stimulation have also been described (83).

2.2.2. Supraspinal Inhibitory Neuroplasticity

Multiple systems have been described producing supraspinal nociceptive inhibition, both tonic and phasic, and originating in the medulla and midbrain (83). As mentioned before, the centres involved (e.g. rostral ventromedial medulla RVM or periaqueductal grey PAG) are often the same ones as those implicated in supraspinal facilitation - albeit involving different spinal pathways and receptor systems (85,86). The type of response involved depends on stimulation characteristics (e.g. intense or weak), sensory test modality (e.g. thermal or mechanical), pathophysiological condition of the organism (e.g. inflammatory or neuropathic, acute or chronic) and neural pathways involved (87). Supraspinal inhibition is considered to operate mainly via cholinergic or monoaminergic neurotransmission and/or neuromodulation at the level of the posterior horn of the spinal cord; particularly more rostrally, GABAergic interneuronal transmission is frequently implicated as well (42,83).

Tonic inhibitory descending controls on convergent spinal neurones have been demonstrated to involve structures both in the rostral and caudal medulla (83,87,88). Descending controls originating in the caudal medulla are mainly triggered directly by nociceptive inputs, while activation of inhibition from the more rostral medulla (e.g. PAG or RVM) may also involve environmental and contextual factors (83,87,88). The RVM contains cells which control nociceptive transmission (50,51,89). Situated mainly in the nucleus raphe magnus, and projecting onto spinal laminae I, II and V, activated “on-cells” facilitate nociception and activated “off-cells” inhibit nociception, with the former being activated indirectly via the PAG by μ-opioid agonists, and the latter directly inhibited by opioids (90). Both these cells types are considered to be implicated in the development of morphine tolerance, with “off-cells” being activated via excitatory amino-acid neurotransmission (51,90,91). The third class of cells present in the RVM, “neutral cells”, is insensitive to opioids, and its role in nociception is unknown at present (90). This PAG-RVM circuit has been shown to contribute to analgesia in humans, with descending inhibition being activated not only by nociception, but also by PAG stimulation, acute stress or the expectation of relief (89). Stress-induced analgesia has been described in least two forms: “opioid” and “non-opioid” (e.g. mediated by NMDA-based mechanisms), with more severe forms of stress being likely to stimulate the latter, and milder ones the former (93,94).

Another well-described supraspinal inhibitory system is that of diffuse noxious inhibitory controls (DNIC) (83,88,95,96). This phasic inhibition is exclusively triggered by nociceptive, heterosegmental afferent A-delta and C-fibre input from parts of the body distant to the convergent spinal posterior horn neurones’ excitatory receptive fields. The resulting powerful inhibition is selective for the wide dynamic range (WDR) spinal con-

vergent neurones and thus can affect both nociceptive and non-nociceptive processing. Structures situated in the caudal medulla (e.g. subnucleus reticularis dorsalis) and separate from those involved in the more tonic inhibitory controls described above are implicated, with the afferent arm of the loop ascending in the ventrolateral, and the efferent part in the dorsolateral spinal funiculi (83,88,95,96). More rostral lesions, such as affecting the PAG, RVM (including nucleus raphe magnus), cuneiform nucleus, locus coeruleus/subcoeruleus, gigantocellular and paragigantocellular nuclei, and the parabrachial area, do not significantly affect DNIC (97,98). A major purpose of DNIC is considered to be improvement of the signal-to-noise ratio between spinal neurone pools activated nociceptively, and those not activated and thus remaining silent, thereby facilitating the extraction and interpretation of nociceptive information (97-100). There is evidence that the acute inhibitory controls elicited by, e.g. inflammation, may decrease with time as inflammation becomes chronic (101-103). Another interesting finding is that, in contrast to other forms of descending inhibition, opioids in the lower dose range interfere with DNIC, via mechanisms at least partially involving the PAG (98), but not directly involving the RVM (104). Thus in this context, supraspinally mediated (low-dose) opioid analgesia would not result from reduced nociceptive inputs, but rather from interferences in the *detection* of nociception via lower nociceptive signal-to-noise ratios due to reductions in DNIC (97,99,100).

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3. PRACTICE - MEASURING NOCICEPTIVE NEUROPLASTICITY IN THE CLINICAL CONTEXT

It may be considered self-evident that an understanding of the mechanisms involved in a disease process involving pain and nociception is fundamental to its effective therapeutic management (1). From the data presented in the previous chapter, nociceptive neuroplasticity is a real potential target for diagnostic measures permitting insight into the pathological mechanisms underlying nociception, and could well provide the basis for the shift from symptom-based to mechanism-based therapeutic approaches in pain medicine (2). A number of questions arise, however, when we start considering nociception and neuroplasticity in the clinical context, i.e. monitoring neuroplasticity in the *individual* patient:

1 How relevant is the question of nociceptive neuroplasticity to the clinical phenomenon of pain?
2 For nociceptive neuroplasticity, can we extrapolate basic research data (e.g. animal models) to the clinical situation?
3 Can we objectively measure nociceptive neuroplasticity in a clinical context?

3.1. Nociceptive Neuroplasticity vs. Pain in the Clinical Context

At present, our understanding of the consequences of nociception in the clinical context is usually based upon the patient's *subjective* pain experience, typically quantified via pain intensity rating, measuring analgesic drug use, or possibly descriptive pain scoring via a questionnaire (3). However, the use of subjective pain experience as a measure of nociceptive neuroplasticity - as opposed to its direct, objective measure - can be expected to be problematic due to the multifaceted and multifactorial nature of the pain experience and its indirect and complex links to nervous system neuroplasticity. In animal models, the connection between neuroplasticity and changes in behaviour following nociception remains ill-defined. Moreover, the relevance of *animal* behaviour to the *human* pain experience is also unclear, further limiting the application of animal nociception research to the clinical situation. In humans, the relationship between clinical pain measures and post-nociceptive neuroplasticity is little investigated, with the research available suggesting varying and generally weak correlations between the two (4-6).

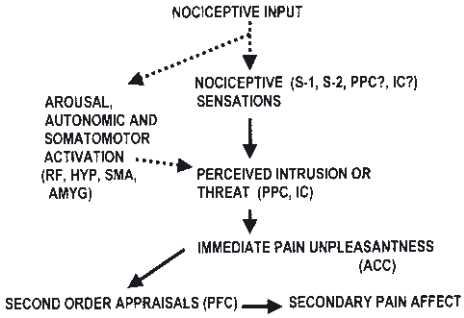

Figure 1: Sensory processing linking nociception, arousal and the pain experience (from reference 7). The CNS structures likely to be involved are given in brackets, abbreviations: PAG = periaqueductal grey, PB = parabrachial nucleus of the dorsolateral pons, VMpo = ventromedial part of the posterior nuclear complex, MDvc = ventrocaudal part of the medial dorsal nucleus, VPL = ventroposterior lateral nucleus, ACC = anterior cingulate cortex, PCC = posterior cingulate cortex, HT = hypothalamus, S-1 and S-2 = first and second somatosensory cortical areas, PPC = posterior parietal complex, SMA = supplementary motor area, AMYG = amygdala, PF = prefrontal cortex.

As described above, nociceptive input undergoes extensive processing before resulting in the subjective experience of pain (figure 1,2). This pain experience includes both sensory (e.g. pain intensity, pain location) and affective (e.g. unpleasantness, suffering) facets, with the latter being further subdivided into primary (immediate implications, e.g. unpleasantness) and secondary (future implications, e.g. suffering) aspects (7). Human subjects can differentiate between the two facets if asked to, and the differential effects of various analgesic drugs on these two facets of pain are well-described (8). Personality traits have been demonstrated to have the least effect on the sensory facet of pain, and the most on the affective facet, particularly its secondary aspects (9,10). The complex path from nociceptive input to the pain experience involves both serial and parallel central nervous system processing (8,11-14). From a number of studies, involving psychophysical techniques as well as functional neuroimaging, we now know that affective aspects of pain are processed in series with (i.e. downstream from) sensory aspects, with parallel processing occurring for arousal and activation of both autonomous and somatomotor nervous systems (15-19). Indeed, the major access of nociceptive spinal posterior horn input to the anterior cingulate cortex, a major centre for integrating attentional and evaluative (e.g. cognitive) factors into overall affective pain valency (and thus response priorities), is indirect, serial and multisynaptic via a ventrally directed somatosensory-limbic pathway (17-20). In contrast, nociceptive spinal posterior horn input has direct, parallel access to lower brainstem and limbic structures mediating arousal and autonomic and somatomotor activation (12-14). Thus it can be expected that the pain experience - particularly its affective facets - will reflect nociceptive input less directly than arousal

and somatomotor/autonomic activation. This will be the more so, the more the pain measure used includes affective facets of the pain experience (e.g. analgesia use or "pain relief" vs. specific pain intensity rating). Furthermore, there is evidence that intensity coding of nociceptive input is well preserved with rostral progression in the central nervous system (16), thus even quite rostral nociceptive neuroplasticity should more directly reflect the intensity of the original nociception than the subjective pain experience.

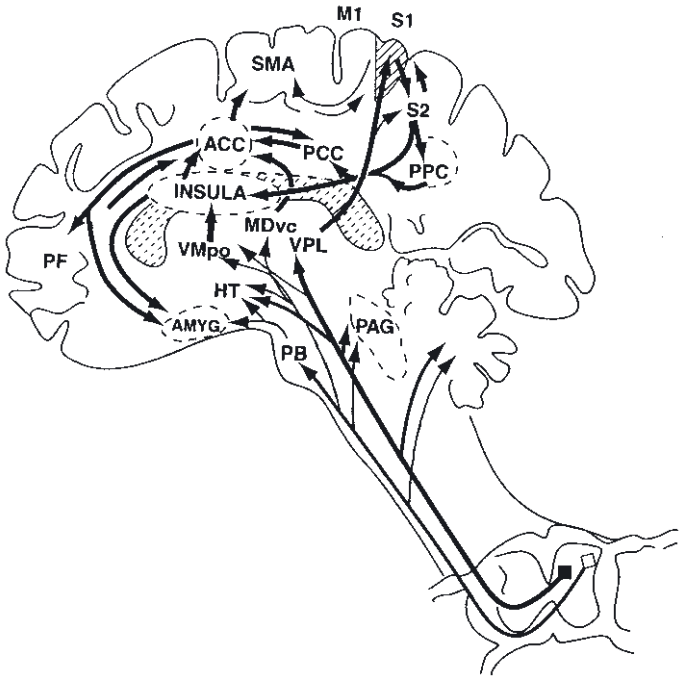

Figure 2: CNS structures involved in processing the subjective pain experience (from reference 7). Abbreviations: PAG = periaqueductal grey, PB = parabrachial nucleus of the dorsolateral pons, VMpo = ventromedial part of the posterior nuclear complex, MDvc = ventrocaudal part of the medial dorsal nucleus, VPL = ventroposterior lateral nucleus, ACC = anterior cingulate cortex, PCC = posterior cingulate cortex, HT = hypothalamus, S-1 and S-2 = first and second somatosensory cortical areas, PPC = posterior parietal complex, SMA = supplementary motor area, AMYG = amygdala, PF = prefrontal cortex.

Taking all of these factors together, present evidence suggests that the relationship between nociceptive neuroplasticity and the clinical pain experience is indirect, weak, and in need of systematic investigation. Furthermore, nociceptive neuroplasticity is potentially a better measure of "nociceptive load" (and the efficacy of its prevention and therapy) than pain. If the outcomes - including pain - of disease processes involving nociception are related to nociceptive load and its modulation, then nociceptive neuroplasticity may prove to be a more useful and informative surrogate endpoint in this respect than pain measures, and potentially interesting for both prognostic and therapeutic application.

3.2. Extrapolation from Animal Models to the Clinical Situation

If data from animal models could reliably be extrapolated to the individual situation of the patient, the need for monitoring nociceptive neuroplasticity in the clinical context would be much smaller. From the account of nociceptive neuroplasticity presented above, a number of inferences can be drawn of relevance to the question of extrapolation. It is obvious that the change in central nervous system processing subsequent to nociception is wide-ranging and complex, involving and integrating both excitatory and inhibitory as well as peripheral, spinal and supraspinal systems. Thus, in view of the high degree of integration and interaction of the systems involved in the response to nociception, observations on the reaction of isolated parts of the nervous system to nociception are unlikely to permit accurate and comprehensive prediction of the reaction of the whole, intact nervous system to nociception. Furthermore, the reaction of the nervous system, particularly the central nervous system, to nociception must be highly dependent on the initial state of the system, both internal and external, making details of the response very specific to the model used. Of note is that this supposition includes the therapeutic consequence that it will be more difficult to restore the activated system to its original state than to prevent this state from occurring. Finally, the nociceptive neuroplasticity actually present will vary according to the timepoint after nociception at which it is observed (i.e. acute vs. chronic neuroplasticity).

These factors taken together suggest that it will be difficult to forecast the integral neuroplastic response of a given patient to specific nociception from data gathered in the animal experimental context (5). This is the consequence of prediction being based upon a different, often non-intact (e.g. spinalised) species of animal, frequently investigated in a different state of health (e.g. otherwise healthy, anaesthetised animal vs. awake human with chronic autoimmune disease), often for a short time span, and many times involving nociceptive stimuli unlike those seen in the clinical context (i.e. electrical C-fibre stimulation vs. fractured bone). As an example of the problems involved, the debate about preemptive analgesia and surgery conducted over the last decade or so has provided us with a graphic illustration of the pitfalls involved in predicting clinical nociception outcomes based on data about nociceptive neuroplasticity in animal models (4).

3.3. Measuring Human Neuroplasticity in the Clinical Context

The desirable transfer from symptom- to mechanism-based pain and nociception management is predicated upon the availability of clinically practicable ways of objectively assessing and measuring nociceptive neuroplasticity in patients. A variety of methods for measuring nociceptive neuroplasticity are at present available in the *experimental* context, involving either neuroimaging, neuroelectrophysiological, or psychophysical techniques. The first two methods have provided much useful, detailed and innovative information regarding nociceptive mechanisms, factors influencing them, and their therapeutic modulation. However, neither method is at present practical for clinical monitoring use in the sense of providing repeated measures of nociceptive neuroplasticity in multiple patients at an affordable price and in a way that is acceptable to the patient.

3.3.1. Functional Neuroimaging Methods

Functional neuroimaging techniques represent the most recent and most sophisticated addition to the armamentarium of methods for following the changes in nervous system function with nociception. They involve making visible the metabolic changes (e.g. blood flow) accompanying central nervous system function, and are either based on radioisotopic methods (e.g. positron emission tomography PET) or magnetic resonance techniques (fMRI) (21,22). Quite a number of studies have appeared over the last years using these techniques to elucidate central mechanisms involved in a variety of pain states. A notable success in this context is the demonstration and elucidation of the cortical neuroplasticity accompanying amputation (23). This is implicated in the pathogenesis of phantom pain after amputation, and institution of various treatment strategies based on (demonstrably) reducing this cortical reorganisation is proving successful in reducing phantom pain. Another pain state in which neuroimaging has made significant contributions to understanding the underlying pathophysiology is migraine headache (24). Neuroimaging studies have provided the means to gain extensive and detailed insight into the alterations of central nervous system function associated with nociception and pain, as well into their therapeutic modulation. However, at present functional neuroimaging is expensive, time-consuming and only performed in dedicated locations, thus making its routine use in the day-to-day clinical context impractical (25).

3.3.2. Neuroelectrophysiological Methods

Neuroelectrophysiological techniques involve the measurement of the electrical activity accompanying nervous system activity (e.g. electroencephalogram EEG or electromyogram EMG), and may be either evoked (a stimulus is presented and the resulting response of the central nervous system quantified; e.g. evoked potentials, evoked reflexes) or passive (observing what happens to the EEG in a particular situation, e.g. event-related potentials). Pain-evoked potentials (e.g. via laser stimulation), RIII-reflex determination (an electrically evoked nociceptive reflex) and EEG arousal reaction (an event-related potential) are classic illustrations of neuroelectrophysiological techniques used in the investigation of pain and nociception (26-28).

Neuroelectrophysiological measures have proven particularly helpful in the investigation of pain and nociception in the context of general anaesthesia, where psychophysical methods (which require consciousness) are impossible to apply. In this context, both the EEG and evoked potentials have been used to detect supraspinal excitation or inhibition following nociceptive input (29,30), with the EEG giving a more holistic picture of the cortical reaction, and evoked potentials looking more at specific pathways and structures. The application of topographic (e.g. mapping, dipole source determination) and temporal (e.g. evoked reactions, signal averaging) techniques has proven valuable when used to determine the pathways and structures implicated in the processing of nociception and pain (29,31). However, the routine clinical application of these techniques is made onerous by their large intra-individual variability in awake subjects and their time-consuming and technically demanding nature. Their most promising clinical use at present is for nociception monitoring during anaesthesia (32).

In the context of investigating spinal nociceptive processing, electrophysiological techniques specifically targeting spinal nociceptive mechanisms have proven to be of particular importance. Given that the study of spinal processing is difficult with psychophysical or neuroimaging approaches, the development of methods such as nociceptive flexion reflexes (e.g. the R-III reflex) (33) has proven invaluable. Unfortunately, as for supraspinal electrophysiological techniques, the application of spinal electrophysiology to routine clinical use is at present not practicable, again due to its time-consuming and technically demanding nature.

3.3.3. Psychophysical Methods

Psychophysical techniques study the relationship between physical stimulation and resulting sensation. They thus detect neuroplasticity via the changes produced in stimulus-response curves, such as the left-ward shift resulting from hyperalgesia. Psychophysical methods are suitable for everyday clinical use as the equipment is portable and not overly complicated, and the protocols involved can be adapted to limit the time necessary to perform them (34). Typical examples in pain research include the determination of thresholds (e.g. pain tolerance threshold) to various stimuli (e.g. electric, mechanical or thermal), and the rating by subjective measures (e.g. pain intensity visual analogue scales) of stimuli of varying intensity (usually above threshold), e.g. in order to obtain dose-response relationships (35). For formal, quantitative testing of somesthetic function (quantitative sensory testing, QST), standardisation and validation of both test stimuli and testing paradigms is of particular importance. Standardised and validated testing protocols were first developed in the context of sensory testing for neurological disease (e.g. diabetic neuropathy), starting over a decade ago (36,37). Since then the application of such protocols has been extended to nociception and pain research by several groups, resulting in a number of protocols for performing quantitative sensory testing in the field of pain research (6,38,39).

For clinical application, a trade-off between accuracy (which lengthens protocols) and practicability (which makes them less comprehensive) has to be made. The data collected should, however, inform about the effects of stimulation modality (e.g. electrical, mechanical, thermal), summation (e.g. temporal, spatial) and topography (e.g. generalised, segmental). To date, quantitative sensory testing has been applied in many clinical experimental contexts including various types of neuropathic pain, complex regional pain syndromes, and soft-tissue/joint disorders such as fibromyalgia or osteoarthritis (36-40). In the future, testing different types of structure (e.g. somatic vs. visceral, superficial vs. deep) will assume increasing importance, although at present this is still very much subject to experimental development.

Transcutaneous electrical stimulation remains a foundation of clinical QST in view of its eminent controllability, ease of use, and extensive as well as long-standing record of validation (41). Its advantages include a) the ability to provide well-defined single and summated stimuli, b) proven sensitivity to excitatory and inhibitory (e.g. DNIC) neuroplasticity, and c) the potential to stimulate of a wide range of tissues (e.g. skin, muscle). Disadvantages include a) the non-physiological nature of the stimulus, and b) the need to adapt existing methods to include a topographical element.

Mechanical stimulation is well-established in practice and includes the use of graded filaments (e.g. von Frey hairs) and pressure algometers (6,39,42). The facts that a) this is a physiological stimulus with proven sensitivity to excitatory neuroplasticity, and b) the filaments are eminently suited to sensory mapping, are clear advantages. However, disadvantages include that a) filaments do not provide pain tolerance thresholds and must be used very carefully to achieve precise, reproducible results, b) pressure algometers are not easily applied everywhere (best over bony prominences), c) mechanical stimulation appears to be less sensitive to inhibitory neuroplasticity than electrical stimulation in the post-surgical context, and d) pressure thresholds are more influenced by gender than others (43).

Thermal sensory testing is at present achieved mainly by Peltier element or laser stimulation and is a traditionally recognised method in pain research (44,45). Both methods have achieved a high degree of sophistication and are frequently used in pain research. The advantages of thermal testing are that it is a) an eminently controllable physiological stimulus, and b) sensitive to excitatory neuroplasticity. The main disadvantage is that it represents a monomodal stimulus highly selective for certain peripheral nerve fibre subpopulations, which might limit its application to the multimodal surgical context.

Thus we have in quantitative sensory testing involving psychophysical methods a defined, validated, practicable and affordable technique with the realistic potential of being applicable to everyday clinical practice for the diagnosis and monitoring of noci-

ceptive neuroplasticity. The different stimulus modalities (i.e. electrical, mechanical, thermal) may be at least partially complementary in the information they provide, with electrical stimulation appearing to provide the most comprehensive coverage at present. Further research is necessary to define the exact differential and comparative usefulness of the various stimulus modalities either alone or in combination.

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4. STUDY GOALS - QUANTITATIVE SENSORY TESTING, ANALGESIA AND NOCICEPTIVE NEUROPLASTICITY

Pain associated with surgery continues to be a major clinical challenge (1). Over 80% of patients in a large British survey reported experiencing significant pain after surgery, and in one third of these patients, such pain was present most or all of the time (2). An American survey of pain and surgery found that postoperative pain was the primary concern of patients preoperatively, and that three quarters went on to suffer significant postoperative pain (3). Apart from the humanitarian obligation of treating postoperative pain, adequate perioperative management of pain and nociception is now accepted to play an important role in reducing postoperative morbidity, improving clinical outcomes and speeding the patient's recovery. A recent large meta-analysis of the intraoperative use of neuraxial anaesthesia, which considerably attenuates intraoperative nociceptive input, has demonstrated reduction of mortality by one-third, together with lower risk of deep venous thrombosis, pulmonary embolism, blood transfusion, pneumonia, respiratory depression, myocardial infarction and renal failure (4). Postoperative neuraxial analgesia has also been demonstrated to be of benefit, particularly regarding pulmonary complications (5). Despite such insight into the importance of perioperative management of nociception and pain, despite considerable advances in understanding nociception and pain mechanisms, and despite improvements in the system for treating postoperative pain (e.g. by introduction of acute pain services), progress in achieving significant advances in perioperative nociception and pain management has been slow.

Management strategies for perioperative pain and nociception have so far been symptom-based (6). Traditionally, postoperative analgesia has been managed by asking the patient about his pain experience. However, the alterations in central nervous system processing (neuroplasticity) associated with surgical nociception are increasingly recognised to play an important role in acute postoperative pain (7). Nociceptive neuroplasticity is also considered to be implicated in pain chronification, and hence to be of relevance to long-term pain outcomes after surgery (7). In addition, as discussed above, nociceptive neuroplasticity may provide a link to other outcomes (e.g. complications) after surgery, particularly via metabolic and immunological mechanisms. Thus an understanding of the neuroplasticity allied with surgery is likely to provide insight into the mechanisms underlying postoperative pain and associated with surgical nociception, offering the basis for a shift from symptom-based to mechanism-based management strategies for perioperative pain.

The detection and diagnosis of surgical nociceptive neuroplasticity is still very much in the early stages of development, with little systematic research having been performed in this area to date. Several promising methods for the quantification of changes in sensory processing are available - and reasonably well-validated - in the experimental arena. However, the transfer of these methods to everyday clinical, surgical use is little investigated and promises to be challenging. Clinical testing for surgical nociceptive neuroplasticity demands both simplicity and rapidity in order to ensure its everyday feasibility.

At the same time, testing must not sacrifice a certain minimum of multimodality in order to do justice to the complexity of surgical neuroplasticity. Taking into account these considerations, it would appear to us that psychophysical methods (i.e. quantitative sensory testing) may provide an attractive approach to the postoperative quantification of nociceptive neuroplasticity (8).

Against this background, the main, overall aim of the research presented here is thus to provide the first basis for a change from symptom-based to mechanism-based management of perioperative pain and nociception. Our plan was to achieve this by using quantitative sensory testing (QST) as a means of exposing the mechanisms underlying perioperative analgesia and pain. This approach has, to date, been rarely applied in the *clinical* context, with a systematic investigation not having been published so far. Section III will provide the introduction to this topic. It covers the feasibility of using QST to quantify pharmacologically induced analgesia and antinociception in healthy persons without the influence of surgery. In section IV we then go on to systematically explore the neuroplasticity resulting from surgical nociception using QST. Furthermore, we study the influence of clinically important factors such as analgesia and preoperative pain on postoperative surgical neuroplasticity.

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III

QUANTIFYING ANALGESIA

5. INTRODUCTION - QUANTITATIVE SENSORY TESTING AND ANALGESIA MEASUREMENT

The purpose of the studies presented in this section is to help us to understand and optimise the performance of quantitative sensory testing (QST) in the human, clinical context by applying it first to the investigation of analgesia before moving on to the more complex issues of monitoring perioperative neuroplasticity. Antinociception and analgesia are an essential part of the anaesthesiological management of surgical nociception and pain. As for surgical nociceptive neuroplasticity, analgesia has generally been quantified up till now in the clinical context by measures of the subjective pain exeprience. Classically, this involves documenting the reduction in pain intensity due to a clinically relevant painful condition induced by analgesic intervention. Again, QST offers the opportunity of obtaining a more objective measure by quantifying the shift in stimulus-effect curves caused by the analgesic intervention (e.g. hypoalgesia to a defined experimental painful stimulus). Thus it seemed logical to us to investigate whether the antinociceptive and analgesic effects of drugs with accepted anaesthetic and analgesic properties could practicably be measured using QST. In particular, we wished to study how such drugs affect QST measures of themselves, before going on to use QST in the more complicated context of studying surgical nociceptive neuroplasticity and it modulation.

Since the first QST publications a quarter of a century ago (1,2) many studies reporting QST use have been published, the bulk of which involve testing in the context of neurological disease (3). The application of formal QST paradigms to pain medicine took place more slowly, with the majority of publications over the last 20 years investigating chronic pain syndromes. Sensory thresholds are the most frequently used QST parameter, but pain report after a fixed, usually suprathreshold stimulus is also used (4). Pain threshold testing to determine analgesic effects of drugs in humans has been practised for at least as long as formal QST testing (5), with a large body of literature (some 250 articles) involving a variety of techniques having been published since.

Quantifying analgesia by means of QST techniques such as threshold testing requires attention to a variety of methodological issues. These include:

1 choice of appropriate stimulus modality (e.g. electrical vs. mechanical)
2 choice of stimulus characteristics (e.g. phasic vs. tonic stimuli, pain detection vs. tolerance)
3 choice of appropriate time-points for measures
4 choice of an appropriate testing paradigm.

For systemic analgesia quantification, topographic considerations are of lesser importance, making the measure of thresholds at multiple anatomical sites unnecessary.

5.1. Stimulus Modality

The choice of stimulus modality is determined by a number of considerations. Mechanical thresholds (pressure pain thresholds) are more influenced by gender than electrical or thermal thresholds (6), and may be less sensitive to direct pharmacological analgesic effects (7). Thermal stimulation is very specific for thin-fibre nociceptive afferents and is eminently controllable and well-validated both via laser and Peltier element application (4,8). With mechanical as well as thermal stimulation it is, however, difficult to produce the intensive and multimodal nociceptive stimuli necessary to model clinically typical nociceptive inputs without permanent tissue damage, and thus to achieve clinical relevance in assessing analgesia. In contrast, electrical stimulation, while not a strictly physiological stimulus, has been demonstrated to be able to produce clinically relevant nociceptive input - including sensitisation - without permanent tissue damage (9). Furthermore, the analgesic effects of analgesic drugs may be modality specific (7). Taking these factors into account, we chose to initially investigate both thermal and electrical stimulus modalities for our experimental analgesia studies.

5.2. Stimulus Characteristics

The major consideration is to use a nociceptive stimulus which has predictive relevance to the clinical situation. Thus phasic and pain tolerance thresholds have more predictive strength than tonic and pain detection thresholds, as the former are more likely to achieve an adequate load of nociceptive input and to stimulate the C-fibres necessary for clinically relevant pain and its consequences (e.g. sensitisation) (10,11). In addition, it is important to include the elements of temporal and spatial summation in the choice of the stimulus, as modulation of summation is important for the clinical effectiveness of analgesia (12,13). Repeated and longer-lasting (tonic) stimuli are thus more likely to predict clinically relevant analgesia than single and short-lasting (phasic) ones. The studies discussed here investigate the effects of a variety of stimulus characteristics in an attempt to understand their applicability to and predictiveness of clinical analgesia.

5.3. Timepoints Of Measures

The timepoints chosen for threshold determination should take into account pharmacological factors, both pharmacodynamic and pharmacokinetic (10). Thus bolus investigations need to include multiple measures, with a higher density at the beginning of the study to include the time of peak concentration, while infusion studies should ideally be performed in steady-state. The need for higher density of threshold measures will of course necessitate the choice of a QST measure that is simple, repeatable and rapidly performed. It is also important to consider the differences between plasma and effect site drug kinetics. We present both a bolus and an infusion study design here as examples of how timepoints of measure might be appropriately chosen in the investigation of experimental analgesia.

5.4. Testing Paradigm

QST results are based on psychophysical responses. They are thus highly sensitive to methodological details and susceptible to a great variety of internal and external environmental influences (3). Therefore due attention must be paid, via strict experimental protocols, to such details in order to achieve acceptable reproducibility and validity of the results (14). In particular, it is important to consider the following points:

1 minimise learning and habituation effects, e.g. via familiarisation and training sessions before any actual study measures are made, e.g. via pseudo-randomisation of stimulus presentation (3,14-16)
2 standardise the environment within which measures are performed, e.g. via standard instructions to subjects (3,14,15)
3 standardise sites of QST testing, e.g. use and mark same stimulation sites throughout study (14,15)
4 use validated testing paradigms, including methods to test for non-co-operation of the patient, e.g. null stimuli (17).

A number of validated testing paradigms are now available (3,14,15), based either on the method of limits (stimulus increases up to threshold, at which time a button is pressed, necessitating consideration of reaction time), levels or staircases (fixed stimuli, increasing or decreasing according to response), or forced choice (subject indicates which of two time epoch contains the target stimulus) (3,14,15).

For the studies presented here, we chose the method of limits, as this type of algorithm is quick and simple to perform with good reliability and validity (14). For thermal testing we used a commercially available computer-controlled system with Peltier thermode, using a well-validated algorithm, and incorporating the desirable design details listed above (15). Electrical testing was performed manually using a standard nerve stimulator and tetanic stimulation via self-adhesive ECG electrodes remaining in situ for the duration of the study, again using a method of limits and incorporating the above design details.

The overall purpose of the studies presented here is as an introduction to the practical use of QST in the context of pain. In particular we consider it important to first understand the effects of analgesic and antinociceptive drugs *by themselves* on QST before going on to study the effects of - and interactions with - surgery. Taking into account the methodological issues detailed above, a major aim was to investigate the practicability and performance of QST when used in the clinical context to study antinociceptive properties of anaesthetic or analgesic drugs. Detailed questions to be addressed by this research included the following:

1 When anaesthetics are used for sedation, do they also modulate nociception, and if so, is this modulation affected by dosage and agent chosen?
2 How do different stimuli perform in demonstrating antinociception by an opioid analgesic, and how do such different measures of analgesic effect relate with plasma pharmacokinetics of the agent?

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6. *Article* - Thiopental vs. Propofol

(Wilder-Smith OH, Kolletzki M, Wilder-Smith CH. Sedation with intravenous infusions of propofol or thiopentone. Effects on pain perception. Anaesthesia 1995;50:218-22)

Sedation with intravenous infusions of propofol or thiopentone

Effects on pain perception

O. H. G. WILDER-SMITH, M. KOLLETZKI AND C. H. WILDER-SMITH

Summary

The aim of this study was to investigate pain perception during thiopentone or propofol infusions for sedation. Thirty ASA 1 or 2 patients received a two step infusion of either thiopentone (step 1: 1.25 mg.kg^{-1} followed by 2.5 mg.kg^{-1}.h^{-1}; step 2: 1.25 mg.kg^{-1} and 12.5 mg.kg^{-1}.h^{-1}; n = 15) or propofol (step 1: 0.5 mg.kg^{-1}, 1 mg.kg^{-1}.h^{-1}; step 2: 0.5 mg.kg^{-1}, 5 mg.kg^{-1}.h^{-1}; n = 15) for sedation. At control and 10 min after the start of each infusion dosage, reaction times and thermal pain detection thresholds were determined. We found no clinically or statistically significant depression of thermal pain detection thresholds during propofol or thiopentone infusions and these are, therefore, unlikely to be associated with clinically relevant hyperalgesia.

Key words

Anaesthetics, intravenous: propofol, thiopentone.
Pain: thresholds.

Subanaesthetic infusions of intravenous agents for sedation during regional anaesthesia, uncomfortable diagnostic procedures (e.g. endoscopies, interventional radiology) or minimally invasive surgery are used increasingly [1, 2]. These infusions increase patient comfort and acceptance of such procedures by inducing sleep, amnesia and anxiolysis. Hyperalgesia in the presence of discomfort and pain from the procedure itself, or from uncomfortable positions, hard tables or trolleys and long-lasting immobility, is clearly undesirable.

Propofol has proved well-suited for use as a continuous intravenous infusion, particularly for sedation [2, 3] but thiopentone infusions are much less frequently used due to less favourable pharmacokinetic properties [4–6]. Barbiturates and propofol have been considered by some workers to be hyperalgesic in small doses [7]. Indeed, with the emergence of new measurement techniques, the discussion on hyperalgesia and intravenous agents has been renewed [7, 8], with both hypo- and hyperalgesic properties being demonstrated for barbiturates and propofol [9–13]. At present no clinical studies of pain perception during sedation by intravenous infusion of anaesthetic drugs are available.

The aim of this study was to investigate pain perception during a two-step, continuous intravenous sedative infusion of either propofol or thiopentone using thermal pain detection thresholds. The main objective was to demonstrate the absence or presence of clinically significant hyperalgesia during such infusions.

Methods

The study protocol was approved by the University of Bern ethics committee. We studied 30 ASA 1 2 patients, aged 17–69 years, scheduled for elective orthopaedic surgery under epidural anaesthesia. Patients with conditions associated with peripheral neuropathy (e.g. diabetes mellitus) or who had other neurological diseases, were not studied. After detailed explanation and informed consent, the patients were prospectively randomly allocated to receive a continuous intravenous infusion of either propofol or thiopentone for sedation. Patients did not receive premedication and did not know which sedative infusion they were allocated.

After establishing venous access and ECG and noninvasive automatic arterial blood pressure monitoring in the anaesthetic room, patients were allowed to rest for 5 min. The subsequent baseline measurements (control) consisted of pulse, arterial blood pressure, reaction time and thermal pain detection thresholds. Sedation was induced by an intravenous bolus of either propofol 0.5 mg.kg^{-1} or thiopentone 1.25 mg.kg^{-1}, immediately followed by an

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infusion of either propofol 1 $mg.kg^{-1}.h^{-1}$ or thiopentone 2.5 $mg.kg^{-1}.h^{-1}$, respectively. A lumbar epidural catheter was inserted using the classical loss of resistance method with the patient in the left lateral decubitus position. A test dose of local anaesthetic (3 ml 2% lignocaine with adrenaline 1:200,000) was injected into the epidural catheter at this stage and the patients were returned to the supine position. Ten min after bolus injection of the intravenous anaesthetic, the same series of measurements carried out for control were repeated (low infusion rate measurements). Twenty min after the initial bolus, patients received a second intravenous bolus of either propofol 0.5 $mg.kg^{-1}$ or thiopentone 1.25 $mg.kg^{-1}$. Simultaneously, the infusion was increased to propofol 5 $mg.kg^{-1}.h^{-1}$ or thiopentone 12.5 $mg.kg^{-1}.h^{-1}$. Ten min later, the last set of measurements (high infusion rate measurements) was performed and the study terminated.

Patients were encouraged to familiarise themselves with the reaction time and pain threshold tests in a learning session just before the study started. Reaction time (RT) was determined in order to control for confounding sedative effects on pain threshold determination and as a gross measure of psychomotor impairment. It was obtained by means of a simple computer programme which generated an acoustic signal (beep) and then measured the time taken to press a button as fast as possible. This was repeated five times and a mean time calculated. Reaction time measures were always performed just before measuring pain thresholds.

The thermal pain detection threshold was measured on the thenar eminence of the dominant hand by a device well validated for pain research (Pathtester, Phywe, Göttingen/D) [14, 15]. For the determination of the pain detection threshold, this device heats a Peltier element under computer control from a baseline temperature of 40 C at a rate of 0.7 $C.s^{-1}$, with a cut-off temperature of 52 C. The subject was asked to press a button, thus stopping further heating, as soon as the sensation of heat just changed to pain. Heating is preceded by an alerting tone and the interval to heating was pseudorandomised between 1 and 3 s by the controlling computer programme to avoid habituation and learning effects. The intertrial interval was 10 s. After three practice attempts, a series of five measurement runs were performed which were averaged to give a mean value. The thermal pain detection thresholds were converted to percentages of maximum possible effect (MPE) according to the following formula:

$$MPE = ((T_{TPDT} - 40):12) * 100$$

where T_{TPDT} is the thermal pain detection threshold measured in C and 12 is the difference between the maximum possible temperature (52 C) and the baseline temperature (40 C).

Data analysis was performed using the computer statistical package *Statistica for Windows* [16]. Physical characteristics and reaction times are expressed as mean (SD) (95% confidence intervals). Pain thresholds are expressed as median (range). The patients' physical characteristics and reaction times were compared using Student's *t*-tests for dependent or independent samples as appropriate. Thermal pain thresholds were compared within groups using Wilcoxon's rank sign test; intergroup comparisons were made using the Mann–Whitney *U*-test. $p < 0.05$ was considered statistically significant.

Results

One patient in the thiopentone group was excluded from analysis because of technical problems with threshold measurement.

Physical characteristics are listed in Table 1 and were similar for the two groups. The haemodynamic values, reaction times and pain thresholds are presented in Table 2. Patients receiving propofol had shorter initial reaction times than those receiving thiopentone ($p = 0.01$) but the control values for the pain detection thresholds were similar (Table 2). Systolic and diastolic arterial blood pressures decreased from control values in both groups but there were no between-group differences.

The changes in thermal pain detection thresholds within the groups compared to baseline were statistically significant only for the high thiopentone infusion rate (Table 2, Fig. 1). At no time were there significant differences between the propofol and thiopentone groups for pain thresholds. Higher infusion rates lengthened reaction times significantly (Table 2, Fig. 2). There were, however, no significant differences between the groups. This remained so when analysing changes in reaction time to try and compensate for the differing initial reaction times. Although thiopentone showed a trend towards larger increases in reaction time for a given increase in pain threshold, this difference was not statistically significant (Fig. 3).

Discussion

To our knowledge, this is the first clinical study to have investigated pain perception during intravenous infusions of anaesthetic agents for sedation. At low and medium infusion rates typically used clinically for sedation [2, 17], we were able to demonstrate the absence of a depression of pain thresholds of statistical or clinical significance. Thus, the perception of pain is not increased during such infusions.

In fact, for the higher infusion rate used in this study, the thiopentone infusion brought about a statistically significant depression of pain perception (pain threshold increase approximately 19%), paralleled by increases in reaction time (94%) as a measure of increasing psychomotor impairment. In comparison, 30 $\mu g.kg^{-1}$ of alfentanil intramuscularly produces a maximum increase of heat (laser) pain thresholds of 116% for an increase in reaction time compared to control of only 10% [18].

The effect of anaesthetic drugs on pain thresholds has been studied for intravenous boli of thiopentone and propofol. Clutton-Brock [9] and Dundee [13] using semi-quantitative pressure algesimetry, found that subhypnotic boli of thiopentone had hyperalgesic effects. Comparing subhypnotic boli of propofol with thiopentone, Briggs and co-workers [10], also using semi-quantitative pressure algesimetry, again found thiopentone to exhibit hyperalgesic actions, whereas propofol produced hypo-algesia.

Table 1. Physical characteristics. Values are expressed as mean (SD) (95% CI) where appropriate.

	Thiopentone	Propofol
Age; years	36 (13.5) (28.2 43.8)	35 (14.3) (26.7 42.6)
Height; cm	174 (8.3) (168.0 179.1)	172 (9.0) (167.0 176.9)
Weight; kg	73 (10.4) (66.8 78.8)	66 (11.1) (60.3 72.5)
Men:women	9:5	8:7

Table 2. Haemodynamic values, reaction times, and thermal pain threshold values in patients receiving thiopentone ($n = 14$) or propofol ($n = 15$) infusions for sedation during epidural anaesthesia.

	Thiopentone	Propofol
SAP; mmHg		
control	140 (12.3) (133–147.6)	138 (17.9) (128–148)
low	131 (12.3) (124–138)*	127 (15.2) (119–136)*
high	123 (9.9) (117 128)*¶	119 (20.5) (108 131)*
DAP; mmHg		
control	86 (9.8) (80 91)	80 (14.4) (72 88)
low	77 (12.6) (70 84)*	73 (10.6) (67 78)
high	69 (8.9) (64 74)*	64 (10.5) (58 70)*
Pulse; beat.min $^{-1}$		
control	70 (13.7) (63–78)	77 (15.9) (68–86)
low	77 (13.3) (69–84)*	83 (10.7) (75 91)
high	78 (10.2) (72.1–83.8)*	84 (10.7) (78–90)
Reaction time; ms		
control	255 (34.4) (235 275)#	224 (25.8) (210 238)
low	326 (202.6) (209 443)	251 (41.9) (228 274)*
high	495 (284.3) (331.3 660.0)*¶	330 (136.1) (254 405)*¶
Thermal pain threshold; % maximum possible effect		
control	73 (39.4–96.0)	76 (61.7–97.8)
low	74 (41.9 99.8)	80 (59.0 91.0)
high	87 (42.0–100.0)*	76 (60.4–97.6)

SAP, DAP = systolic, diastolic arterial blood pressure.
Values for SAP, DAP, pulse rate, reaction times are mean (SD) (95% CI). Thermal pain detection threshold is median (range).
'low', 'high' represent measurements taken 10 min after the start of low and high infusion rates of the two drugs (see text).
* = $p < 0.05$ vs control; ¶ = $p < 0.05$ vs low infusion rate; # = $p < 0.05$ vs propofol group.

Robson and colleagues [12], comparing two different methods of algesimetry in investigating the effects of thiopentone, again found thiopentone to be hyperalgesic using pressure algesimetry, but hypo-algesic using simple thermal stimulation with a heated platinum wire. Using argon laser algesimetry to determine thermal pain detection thresholds during subhypnotic boli of thiopentone (0.5 mg.kg $^{-1}$) or propofol (0.25 mg.kg $^{-1}$), Anker-Møller and colleagues [11] also found both propofol and thiopentone to have hypo-algesic effects.

The quoted studies [11, 12] using thermal stimuli agree with ours in finding small doses of barbiturates or propofol to be neutral or hypo-algesic. The differences between these and ours are mainly quantitative and are most likely to be the result of differences in plasma and biophase levels present at the time of measurement [19]. Interestingly, these results are in agreement with recent experimental work showing both propofol and barbiturates to inhibit spinal nociceptive transmission, with no evidence of facilitation, even at the smallest doses [7].

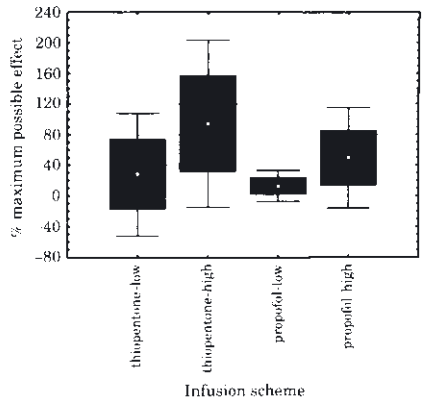

Fig. 1. Box plots of the median percentage change in pain thresholds compared to control, expressed as percentage of maximum possible effect at low and high infusion rates. ■, 95% CI; ⊓, mean; ⊥, SD

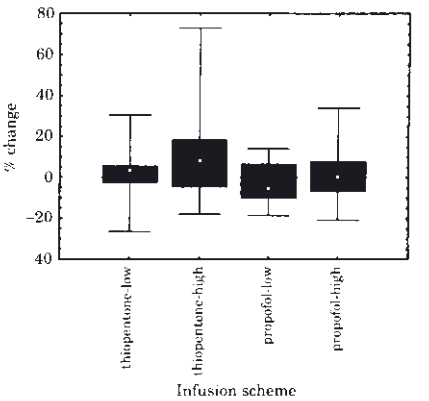

Fig. 2. Box plots of the mean percentage change in reaction time compared to control at low and high infusion rates. Symbols as for Figure 1.

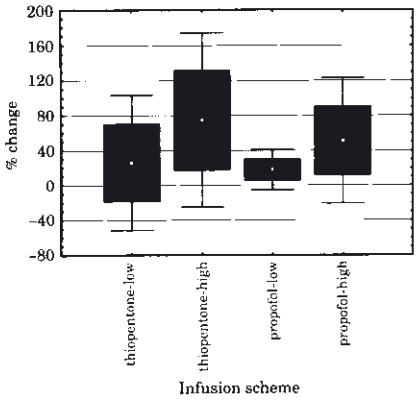

Fig. 3. Box plots of the mean percentage change, compared to control, in reaction time to pain threshold ratios at low and high infusion rates. Symbols as for Figure 1.

The differing, in part, opposing, results of using mechanical and heat stimuli for pain threshold determination are increasingly known and described [15]. They are generally considered to be due to the fact that mechanical stimulation is much more polymodal in nature, making the production of a 'pure' nociceptive stimulus much more difficult and allowing the introduction of multiple confounding factors [15, 20]. In addition, mechanical stimulation remains much less well validated than thermal or even electrical stimulation for pain research [15, 21–23].

The infusion schemes were chosen to reflect typical clinical practice for intravenous sedation [3, 5, 17]. We chose dose ratios (propofol:thiopentone = 1:2.5) generally considered approximately equipotent in clinical anaesthetic practice [24]. However, from our results it would seem that equipotency for the induction of clinical anaesthesia does not correspond to equipotency for reaction time or pain thresholds during sedation.

The pain detection threshold, generally considered to be a good measure of acute pain processing [19, 25], has been determined in a number of ways, including skin heating [15, 20], transcutaneous electric stimulation [26] or mechanical stimulation [21–23]. These methods can give conflicting results under similar conditions, complicating the comparison of results obtained by different methods. This is because these different methods neither stimulate the same range of nociceptive and non-nociceptive receptors, nor activate peripheral nociceptors in exactly the same way [15]. We chose thermal stimulation because it is well-validated and standardised [14], has been shown to be of relevance in investigations of clinical pain [15], and is generally considered to produce the purest monomodal nociceptive stimulus [15, 20].

Heat pain threshold determination by skin thermode may be influenced by a large number of factors such as changes in the subject's reaction time, site of measurement, speed of thermode heating, application pressure of the Peltier thermode and learning and habituation effects [14, 15]. In this study, the largest mean increase in reaction time (thiopentone group) was from 0.255 (baseline) to 0.495 (high infusion rate; Δ-0.240 s). Such a prolongation would have added 0.168°C (=1.41%MPE) to the pain threshold, a change without effect on the statistical analysis. The measurement site and speed of thermode heating were fixed in our study. The Pathtester standardises the thermode application pressure with a spring-loaded arm for the Peltier element. The computer programme controlling the measurement algorithm has been extensively validated and provides for trial runs and pseudo-randomisation of the stimulus-heating interval to minimise learning and habituation effect [14, 15].

In conclusion, we were able to demonstrate that infusions of thiopentone or propofol at doses typically used for clinical sedation are not associated with hyperalgesia. For the regimens used, thiopentone had the larger hypoalgesic effect, associated, however, with more psychomotor impairment than for propofol.

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7. *Article* - Morphine-6-Glucuronide

(Buetler TM, Wilder-Smith OH, Wilder-Smith CH, Aebi S, Cerny T, Brenneisen R. Analgesic action of i.v. morphine-6-glucuronide in healthy volunteers. Br J Anaesth 2000;84:97-9)

Analgesic action of i.v. morphine-6-glucuronide in healthy volunteers

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The pharmacodynamics of morphine-6-glucuronide (M-6-G) i.v. were assessed in 12 healthy male volunteers in an open study. After a single bolus dose of M-6-G 5 mg i.v., we measured antinociceptive effects, using electrical and cold pain tests, and plasma concentrations of M-6-G, morphine-3-glucuronide (M-3-G) and morphine. Pain intensities during electrical stimulation (at 30, 60 and 90 min after injection) and ice water immersion (at 60 min) decreased significantly ($P \leq 0.005$) compared with baseline. Mean plasma peak concentrations of M-6-G were 139.3 (SD 38.9) ng ml^{-1}, measured at 15 min. Our data demonstrate that M-6-G has significant analgesic activity.

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The major metabolites of morphine are morphine-6-glucuronide (M-6-G) and morphine-3-glucuronide (M-3-G).[1] M-6-G has a 100-fold higher affinity for μ opioid receptors compared with morphine when given intrathecally, and shows analgesic activity.[2] Systemic M-6-G has been shown to be approximately equipotent to morphine with respect to analgesic activity but with fewer side effects.[2] However, a recent study failed to demonstrate analgesic activity of M-6-G i.v. in healthy volunteers.[3] In this study, we have examined the analgesic activity of M-6-G i.v. in human volunteers using opioid sensitive pain tests, and related this to plasma concentrations.

Methods and results

After obtaining approved from the Ethics Committee of the University of Berne and written informed consent, we studied 12 healthy male volunteers (aged 21–46 yr, weight 53–80 kg) in an open study. Before injection of M-6-G, a baseline blood sample was obtained from the right antecubital vein and control pain tests conducted. After a light standardized meal, M-6-G 5 mg (Lipomed, Allschwil, Switzerland; >98.5% HPLC purity), dissolved shortly before use in sterile isotonic saline 5 ml, was injected as an i.v. bolus dose over 1 min. Blood samples were obtained every 15 min for the first 2 h and then hourly until the end of the study (5 h). One subject received M-6-G 10 mg and another subject 20 mg orally.

Subjects were instructed in detail concerning the pain tests and a practice run was performed before actual data collection. During testing, subjects were in a quiet, warm room, in a comfortable sitting position. Two standardized tests were performed. In the ice bucket pain test, the non-dominant hand was immersed in an ice water bath maintained at a constant temperature of 4°C and pain intensity was noted after 170 s on a 100-mm visual analogue scale (VAS: 0=no pain, 100=unbearable pain). In the electrical pain stimulation test, the pain tolerance threshold was determined by increasing the current applied with an electrical nerve stimulator (100 Hz tetanic stimulation, Digistim, Biometer A/S, Copenhagen, Denmark) to the thenar eminence of the dominant hand by 0.1 mA s^{-1} until the pain sensation became 'intolerable'. Prior reduction of skin resistance was ensured by degreasing and scrubbing the skin with emery paper. The tolerance threshold current was applied on two occasions for 30 s and pain scores were noted on a VAS. Both pain tests were performed 10 min before and 30, 60, 90, 120, 180 and 300 min after injection of M-6-G. Side effects were noted.

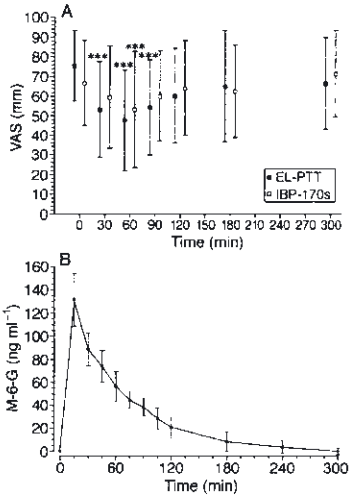

Fig 1 Antinociceptive effects and plasma concentrations of M-6-G. A: Mean (SD) visual analogue pain scores (VAS) of pain intensity (0=no pain, 100=unbearable pain) during ice bucket immersion and electrical stimulation at 200% pain tolerance thresholds in 12 healthy volunteers. EL-PTT=Electrical pain tolerance thresholds, IBP-170s=ice bucket pain test lasting 170 s. ***P<0.001 vs pre-M-6-G baseline. B: Mean (SD) plasma concentrations of morphine-6- glucuronide (M-6-G).

Statistical analysis was performed using analysis of variance (ANOVA) and *post hoc* Tukey's honest significance test. $P<0.05$ was considered significant.

Concentrations of M-6-G, M-3-G and morphine in plasma were assayed by high-pressure liquid chromatography with diode-array detection (HPLC-DAD).[4]

All 12 volunteers completed the pain tests. There were no serious or objective side effects. Subjective effects were sensations of heaviness, warmth and faster pulse (12 of 12 subjects), nervousness (seven), shortness of breath (three) and localized rash (three).

The time–effect for pain intensities during both the ice bucket and electrical pain tests was highly significant ($P<0.0001$) (Fig. 1A). Pain intensities during electrical stimulation were significantly lower than baseline at 30, 60 and 90 min after administration of M-6-G ($P<0.0005$). With the ice bucket test, pain intensity at 60 min was significantly lower than that at baseline ($P=0.004$). At other times differences were not significant. In two subjects who received oral M-6-G, no effects on nociception were observed.

M-6-G was present in plasma only after i.v. administration. Peak plasma concentrations of M-6-G of 90–228 ng ml^{-1} (mean 139.3 (SD 38.9) ng ml^{-1}) were measured at 15 min (Fig. 1B). Morphine was not detectable.

Comment

We have demonstrated that M-6-G has analgesic activity in human volunteers after i.v. application when appropriate and sensitive pain tests are used, corroborating earlier studies in patients and healthy subjects.[2] In contrast, a recent placebo- and morphine-controlled study[3] reported a lack of analgesic activity after constant infusion of M-6-G, although steady-state M-6-G plasma concentrations (70–175 ng ml^{-1}) were similar to those in our study (90–228 ng ml^{-1}). However, the study of Loetsch and colleagues[3] must be interpreted with caution because of the very high incidence of opioid effects and use of naloxone and antiemetics almost exclusively in the morphine group. The resultant unblinding may have prejudiced volunteer reactions and it is possible that the rescue medication itself had effects on nociception. Moreover, the pain-evoked cerebral late potentials used in their study are recognized to be multifactorial in origin and cannot be assumed to measure sensory discriminative responses to pain, but rather reflect emotional–motivational aspects of pain.[5] Late potentials of this type are particularly sensitive to non-analgesic sedation, as seen in the morphine but not in the M-6-G or placebo groups in the study of Loetsch and colleagues.

Because of the difficulties of true blinding in opioid medication groups, we chose an open study design. The choice of tests for demonstration of opioid analgesia is crucial, as phasic, mainly A-δ fibre activating stimuli, as used by Loetsch and colleagues, have been shown to be insensitive for this purpose.[6] The tonic and suprathreshold pain tolerance tests in our study were chosen to ensure activation of C-fibres sensitive to opioid effects. Although qualitative responses to electrical and cold pain stimulation were similar, the former is a multimodal stimulus and the latter probably monomodal. Clinical studies with patients are now necessary to further evaluate the therapeutic potential of M-6-G.

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8. SUMMARY - USING QUANTITATIVE SENSORY TESTING FOR QUANTIFYING ANALGESIA

The studies presented here (1,2) confirm the feasibility of quantifying drug-induced antinociception and analgesia in human subjects using QST. This is in agreement with the literature already available on this topic. Both thermal and electrical pain threshold testing appear to be suited to this task, and it seems possible to adapt the paradigms to investigations under bolus as well as infusion conditions. We were able to teach the paradigms used to naive subjects within about 15 minutes, and the procedure was well-accepted by those taking part in the studies. The tests proved stable and reproducible over the study periods (maximum variability of ca. 20% between measures), suggesting that these procedures might be used to investigate routine clinical surgical patients with only minimal simplification and adaptation. Thus the use of these QST paradigms for simpler experimental analgesia studies in humans provided us not only with specific data on the antinociceptive characteristics of the drugs studied, but also with valuable experience and insight for their subsequent utilisation in the more complex context of clinical surgery.

8.1. QST and Sedation by Anaesthetic Drugs

Our study involved the use of an infusion of two frequently-used intravenous anaesthetic drugs, thiopental and propofol, to sedate patients before surgery. Nociceptive processing was studied by QST using thermal stimulation via a Peltier element. Two approximately stable and *hypnotically* equipotent plasma levels were compared, corresponding to typical light and moderate sedation. The rationale for studying nociceptive processing in this context is that such sedation has often been accused in the literature of causing hyperalgesia (i.e. increased sensitivity to pain), which would of course be undesirable for surgery.

Our prime finding is that neither light nor moderate infusion sedation was associated with hyperalgesia for both propofol and thiopental. In fact, moderate sedation with thiopental produced statistically and clinically significant depression of pain processing by almost 20%. The difference between anaesthetic and analgesic drugs is clearly illustrated by the relationship between sedation (as measured by reaction time) and antinociception (as measured by threshold depression): for thiopental (moderate sedation), reaction time increased by 94% for a decrease in threshold of 19%, for alfentanil (30µg/kg i.m.) reaction time increases by 10% for decrease in threshold of 116%. Despite expectations that propofol would prove to have a better analgesic potency for a given hypnotic potency in comparison to thiopental, this proved not to be the case in this study. Of interest was also the fact that, for both anaesthetics, measures of antinociceptive potency increased more slowly than measures of hypnotic potency with increasing dosage.

Thus this first study using QST during infusion sedation by intravenous anaesthetics not only demonstrated that its use was practicable in this context, but also provided valuable insight into the drugs' antinociceptive properties and their relationships to hypnotic potency at differing doses. In particular, we were able to demonstrate that dose-response

relationships differ between different anaesthetic drugs, not only for antinociception/sedation relationships but also for the individual endpoints of sedation and antinociception, as also suggested by other studies (3,4).

8.2. QST Variables and Opioid Analgesia

The background to this study was the inability of certain authors to formally demonstrate analgesic properties for morphine-6-glucuronide in the experimental context. In our view, the studies unable to demonstrate morphine-6-glucuronide analgesia chose QST variables inappropriate for quantifying opioid analgesia, using phasic, subthreshold stimulation and too unspecific pain effect measures (e.g. pain-evoked cerebral late potentials). We also wished to document plasma concentration-analgesia relationships for intravenous application and investigate if oral application could be effective.

The prime result of our study is to demonstrate that opioid analgesia, in particular morphine-6-glucuronide analgesia, can be reliably quantified over time by QST using tonic, suprathreshold stimulation and repeated visual analogue scaling. In this context, electrical stimulation - despite its “non-physiological” nature - proved more sensitive than thermal (cold) stimulation using ice-water bucket immersion. There was a time lag of about 45 minutes between peak plasma concentration and peak biophase effect (as measured by reduction in evoked pain VAS), suggesting slow penetration into the analgesic central biophase from the circulation. The oral application of 10 and 20 mg morphine-6-glucuronide proved ineffective, resulting in neither measurable plasma levels nor alterations in evoked pain VAS. It should be noted in this context that subjects found suprathreshold stimulation more disagreeable than threshold determination.

The present study highlights the importance of choosing appropriate QST paradigms and stimuli if analgesic effects are to be consistently demonstrated and followed. In the context of opioids, this means giving preference to tonic and suprathreshold stimuli. It is of practical and clinical interest that the pharmacodynamics of opioid analgesia can reliably be quantified and followed using the QST paradigms detailed here, and that the pharmacodynamic time course can lag substantially behind the pharmacokinetic time course.

8.3. Implications for QST and Surgical Neuroplasticity

Our experience from the studies discussed above led us to make a number of modifications for the surgical neuroplasticity QST paradigms. The major changes were that we 1) preferred threshold determinations to methods involving the use of pain report to fixed suprathreshold stimuli, as the former were more acceptable to subjects and were less subject to variability, 2) concentrated on tonic/pain tolerance thresholds, as these appeared more sensitive to changes than phasic/pain detection thresholds, and 3) decided not to use the ice-water immersion test as it was time-consuming, considered unpleasant by the subjects, and less sensitive than electrical skin stimulation to nociceptive modulation. From the pilot tests involved in these studies, we also learnt the importance of adequate time spacing of the tests in order to avoid sensitisation and interference

between measures. While we were of the impression that thermal testing QST paradigms were more onerous to perform than the electrical ones, the difference was not sufficiently large for us to completely abandon thermal testing, particularly the computer-controlled, well-designed and validated testing paradigm in conjunction with electronic data collection used in the first study (5,6).

Taking all of these results together, we suggest that QST, in particular thermal or electric threshold testing, showed potential for the investigation of nociceptive processing modulation by drugs of known antinociceptive potency in humans, and commonly used in the anaesthetic and surgical environment. Thus these studies prepared the ground for investigating such QST paradigms in the context of perioperative alterations of nociceptive processing (i.e. surgical neuroplasticity).

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IV

STUDIES: POSTOPERATIVE NEUROPLASTICITY

9. INTRODUCTION - SYSTEMATIC INVESTIGATION OF SURGICAL NEUROPLASTICITY BY QUANTITATIVE SENSORY TESTING

First attempts to use formal quantitative sensory testing (QST) to investigate neuroplastic changes after human surgery began about a decade ago. A number of studies have been published since then (1-10), with the majority involving the use of mechanical thresholds (1-6,8,10), a couple applying electrical stimulation in combination with other electrophysiological measures (7,9), and one study utilising thermal stimulation via a Peltier thermode (10). To date, only two of these studies have studied post-surgical neuroplasticity in a more detailed fashion by including both a longer time course (i.e. repeated measurements over 7-8 days postoperatively) and investigation of the anatomical distribution of sensory changes (i.e. primary versus secondary hyperalgesia vs. distant sites) (1,2). The other studies cited generally embrace a time course of maximally 48 hours, and often only comprise one or two measures in space and time.

In the studies involving mechanical stimulation, pressure pain thresholds (1,3-6,8) tend to be used more often than von Frey monofilaments (2-4,10). This is because, with regard to nociception, von Frey hairs produce minor, punctate stimulation at best involving A-delta fibres, whereas pressure algometry can be used to determine both pain detection (A-delta fibre) and pain tolerance (C-fibre) thresholds. Most of the studies using mechanical stimulation have determined thresholds at predetermined sites, but one study has introduced the alternative technique of using von Frey hairs to map the area of punctate hyperalgesia surrounding the site of surgery (i.e. secondary hyperalgesia due to central sensitisation) and to assess wind-up pain due to temporal summation of stimuli (2).

Pressure algometry has been most frequently used to quantify primary hyperalgesia (wound tenderness) by measuring directly on the surgical incision (1,3-6,8). Taken together, the studies cited show decreased pressure pain detection thresholds at the surgical site up to 96 hours postoperatively (1), with one study even reporting the persistence of primary hyperalgesia 3 months postoperatively (3). The degree of threshold reduction appears to correlate with the total PCA morphine consumption at 24 hours postoperatively (3). Primary hyperalgesia is unaffected (dextromethorphan (3), tenoxicam (5)) or only very weakly affected (morphine (8)) by perioperative analgesia. One study also looked at secondary mechanical hyperalgesia, which tends to decrease with distance from the wound, and whose time course parallels that of the primary hyperalgesia present up to 4 days postoperatively (1). The same study found no threshold changes distant to the site of surgery (1), suggesting that mechanical thresholds may be relatively insensitive to inhibitory neuroplasticity, in keeping with other evidence (11,12).

For the reasons discussed above, the use of von Frey hairs for threshold determination in the context of surgical nociception has not proven very successful (4,11). They have,

nevertheless, proven useful for mapping as well as for detecting the mechanical hyperalgesia and allodynia surrounding surgical incision (2,3). Using von Frey hairs in this way, it has been shown that the pre- and intraoperative use of a low-dose ketamine infusion significantly reduces the area of secondary hyperalgesia surrounding surgical incision vs. placebo, as well as reducing allodynia in this area (2). This effect lasted for up to seven days postoperatively, without a ketamine effect on primary hyperalgesia. Another such study used von Frey hairs to measure postoperative primary wound hyperalgesia, with the result that dextromethorphan - also an NMDA receptor antagonist - given preoperatively was again unable to reduce primary hyperalgesia compared to placebo (3).

Two early studies have used electrical skin stimulation together with electrophysiological measures to quantify post-surgical neuroplasticity once at a single site 2-3 days postoperatively (7,9). The earlier one discovered evidence of inhibitory neuroplasticity compared to subjects not having undergone surgery via raised sensation thresholds and decreased somatosensory evoked potential amplitudes at a site distant to surgery (9). These results would tend to support other evidence that dermatomal electrical stimulation is sensitive to inhibitory neuroplasticity. Using direct electrical stimulation of the sural nerve, another investigation found lowered pain detection thresholds after surgery compared to non-operated volunteers, accompanied by a trend to decreased nociceptive flexion reflex (R-III reflex) thresholds (9). Thus direct electrical nerve stimulation appears to be much less sensitive to inhibitory controls, reflecting spinal central sensitisation more directly.

Thermal thresholds are considered to be particularly selective for the thin nerve fibres (A-delta, C) relevant to nociceptive input (13). At present we have found only one study using thermal thresholds in the surgical context (10). This study reveals the presence of primary and secondary thermal hyperalgesia around the site of surgery up to six hours postoperatively. Both primary and secondary early postoperative *thermal* hyperalgesia are absent in patients given dextromethorphan preoperatively, with von Frey hair testing being unable to detect a difference in *mechanical* hyperalgesia between the drug groups.

Most of the studies quoted in the present discussion have not been able to demonstrate a tight relationship between clinical measures of pain (e.g. pain scores, analgesic consumption) and measures of surgical neuroplasticity (e.g. quantitative sensory testing). If there is a relationship between pain and neuroplasticity, primary hyperalgesia (which is of peripheral origin) would appear to have the strongest effect, with this effect being maximal during the first postoperative hours. Two studies suggest that primary hyperalgesia has a formal, weak to moderate relationship with postoperative pain scores at rest or during coughing (1) or with postoperative patient controlled morphine consumption (3). As mentioned before, it should be noted that primary hyperalgesia has been shown to be quite resistant to various forms of perioperative analgesia (3-5,8).

Based on the articles above, we would summarise what is known about surgical neuroplasticity as follows:

1 Primary hyperalgesia of the surgical incision (which is of peripheral origin) to mechanical and thermal stimuli is better investigated and can be demonstrated up to 3 months postoperatively. More studied than secondary hyperalgesia of central origin, it appears to have a weak to moderate relationship to clinical pain measures, but is generally quite resistant to (systemic) perioperative analgesic measures.
2 Secondary hyperalgesia next to surgical incision (which is of central origin) can be demonstrated postoperatively for mechanical (up to 96 hours) and thermal stimuli (up to 6 hours). Secondary mechanical hyperalgesia area size and degree of allodynia are significantly reduced by NMDA blockade with ketamine (2), while dextromethorphan reduces thermal secondary hyperalgesia - but apparently not mechanical hyperalgesia (10).
3 Distant to the site of surgery, postoperative sensory testing involving electrical stimulation suggests the presence of central inhibitory mechanisms in the presence of central spinal excitatory neuroplasticity at single times and sites (7,9).

From the above summary, the need for the systematic application of quantitative sensory testing (QST) to investigate human post-surgical neuroplasticity in an integrated fashion is evident. In particular, the *central nervous system (CNS)* plasticity accompanying surgery remains largely unstudied, particularly regarding:

1 the feasibility of using QST to monitor surgical neuroplasticity in the everyday clinical context
2 the detailed nature and time course of the neuroplastic response
3 the modulating effect of typical clinical factors on such neuroplasticity
4 the relationship between surgical neuroplasticity and clinical pain measures.

Regarding the nature of the alterations in CNS sensory processing after surgery, we need to address the details of excitatory vs. inhibitory neuroplastic reactions and the differential contributions of supraspinal vs. spinal mechanisms to these responses. The typical clinical modulating factors which would benefit from study include both intrinsic (e.g. preoperative pain) and extrinsic factors (e.g. perioperative analgesic management).

The scheme for our clinical QST paradigms for surgical neuroplasticity was designed to answer the questions discussed above and based upon experiences with analgesia quantification (cf. section III). It takes the following criteria into account:

1 simplicity (i.e. needing only minimal patient training, ca. 15 minutes)
2 rapidity (testing can be completed in ca. 15 minutes)
3 reproducibility (less than 20% interindividual variability)

4 validation in published literature
5 multimodal testing (sensation, pain detection, pain tolerance)
6 multiple sites (sites close to and far from surgery).

In the first phase of our investigations, we used thermal stimulation for QST due to its nociceptive specificity and the availability of a well-validated testing device (14). However, its use proved to be onerous in everyday practice, and we thus, in the second phase, went on to test a paradigm based on thresholds to *electrical* skin stimulation. To implement this paradigm we used a relatively simple device, which proved well-suited to clinical employ.

The major aim of the study series presented here is to initiate systematic study of the neuroplasticity following surgical nociception. We are specifically interested in the feasibility and practicability of using QST for this purpose in the clinical environment. Specifically, the aim of the study series presented here was to address, using QST, the following questions about human post-surgical central neuroplasticity:

1 What is the nature and time course of post-surgical neuroplasticity?
2 How do a) analgesia and b) preoperative pain affect postoperative neuroplasticity?
3 What is the relationship between postoperative neuroplasticity and clinical pain measures?

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10. *Article* - Epidural Sufentanil

(Wilder-Smith CH, Wilder-Smith OH, Farschtschian M, Naji P. Epidural droperidol reduces the side effects and duration of analgesia of epidural sufentanil. Anesth Analg 1994;79:98-104)

Epidural Droperidol Reduces the Side Effects and Duration of Analgesia of Epidural Sufentanil

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The postoperative combination of epidural sufentanil and epidural droperidol was assessed in 40 patients with hip or knee arthroplasties. Patients were given a single intravenous (IV) bolus of sufentanil 50 μg with either droperidol 2.5 mg or placebo (0.9% NaCl) epidurally in a double-blind, randomized design at the first request for postoperative analgesia. Pain scores, side effects, and sufentanil plasma concentrations were regularly assessed for 5 h after injection. Heat pain thresholds were measured pre- and postoperatively. The incidence of nausea, emesis, and pruritus associated with epidural sufentanil was decreased by epidural droperidol ($P < 0.01$, $P < 0.001$, $P < 0.05$, respectively). More patients were sedated with epidural droperidol than with placebo ($P < 0.02$). The initial reduction in pain scores was similarly profound, but the duration of analgesia after sufentanil and droperidol was significantly shorter than after sufentanil and placebo ($P < 0.02$). Phasic and tonic heat pain thresholds were increased postoperatively 1 h after sufentanil and placebo ($P < 0.01$ and $P < 0.0005$, respectively). Only the tonic heat pain thresholds were increased 1 h after sufentanil and droperidol ($P < 0.002$). The addition of epidural droperidol significantly reduced the excitatory side effects of epidural sufentanil while diminishing the duration of analgesia. These interactions may be of clinical significance in reducing the toxicity of opioids, but the effect on duration of analgesia must be considered when repeated doses of opioids are prescribed.

(Anesth Analg 1994;79:98–104)

Sufentanil is a potent analgesic used epidurally, intrathecally, and intravenously in the management of perioperative pain (1–3). It is a highly selective μ receptor agonist, with corresponding side effects. The opioid side effects, such as nausea, emesis, pruritus, hypotension, respiratory depression, and urinary retention can markedly offset the advantages of improved postoperative analgesia. Neuroleptic drugs have antiemetic and cardiovascular-stabilizing properties, as well as analgesic characteristics (4–6). The combination of opioids and neuroleptic drugs is routinely used perioperatively, as well as in pain related to neoplastic disease (7,8). In a previous study, the epidural combination of droperidol 2.5 mg and morphine in the postoperative period resulted in a significantly reduced incidence of side effects (9). The effect of the addition of droperidol on morphine analgesia was difficult to assess because of the great variability and the long duration of morphine analgesia. In this study, the more potent, μ receptor-specific and shorter-acting opioid, sufentanil, was used to assess the interaction with droperidol. Sufentanil was given epidurally because a catheter was *in situ* for intraoperative local anesthetic administration and because of the increased acceptability compared to intrathecal use. Additionally, an important part of the analgesic action of opioids is mediated spinally (10).

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Methods

Forty successive patients were included in this randomized, double-blind comparison of the epidural combination of sufentanil with either placebo or droperidol for postoperative analgesia. The patients gave oral informed consent, and the study was approved by the University Hospital Ethics Committee. All patients were ASA grades I-III, undergoing elective total hip or knee replacement surgery (20 each). Specific exclusion criteria were previous opioid medication, epilepsy, renal failure, diabetes, neuropathies,

excessive blood loss or other intraoperative complications, and the usual contraindications for epidural anesthesia.

After premedication with midazolam 7.5 mg *per os* 30–45 min preoperatively and infusion of 1000 mL lactated Ringer's solution, all patients had a standardized epidural anesthesia at L2–3, L3–4, or L4–5. The loss-of-resistance method was used to locate the epidural space in the lateral recumbent position. Lidocaine-CO_2 2% (without epinephrine) 3 mL (Sintetica; Mendrisio, Switzerland) was given as a test dose. After insertion of the epidural catheter, the second 3-mL dose of lidocaine-CO_2 and, 5 min later, the first half of the dose of lidocaine-CO_2 calculated according to weight, age, and extent of block were injected (11). Sixty minutes later the second half of the lidocaine-CO_2 dose was given. The total dose of lidocaine-CO_2 given ranged from 18 to 24 mL, the mean dose being 20 mL. Postoperatively in the recovery room, patients were given the study drug from coded ampules as a single bolus via the epidural catheter at the first request for analgesia. Sufentanil 50 µg and placebo (NaCl 0.9%) or sufentanil 50 µg and droperidol 2.5 mg were given epidurally in a total volume of 10 mL. After the single dose of epidural study drug, all further analgesia was performed "on-demand," when patients demanded additional pain medication, with metamizole 1 g intravenously or nicomorphine 0.1 mg/kg subcutaneously. All epidural procedures were performed by the same two anesthesiologists.

Documentation throughout the study was done by one research nurse, who observed the patient from admission to discharge. Pain intensity (verbal rating scale [VRS] 0–4, 0 = none, 4 = unbearable), nausea (VRS 0–4), sedation (nurse observation: 0 = spontaneous communication, not sleepy; 1 = slightly sleepy, spontaneous communication; 2 = responds to verbal commands, no spontaneous communication; 3 = only responds to physical contact, no spontaneous communication; 4 = no response, even to physical contact), emesis (number of episodes, including retching), shivering (nurse observation 0–4), pruritus (VRS 0–4), and side effects, specifically extrapyramidal signs, were documented before and every 15 min for the first hour, and then hourly until 5 h after study drug application. Arterial blood pressure and heart and respiratory rates were monitored at the same times. Hypotension was defined as a decrease of more than 20% of the mean arterial pressure compared to the pressure just before study drug injection. Oxygen saturation was recorded by continuous pulse oximetry for the first 6 h postoperatively. Oxygen was administered by nasal cannulae if O_2-saturation decreased to less than 90%. The time to add-on analgesia was noted. At the end of the study, patients rated the quality of analgesia as inadequate, good, or excellent. Blood was drawn from a forearm vein for determination of sufentanil plasma concentrations before and 15, 45, 90, 180, and 300 min after study drug administration. Sufentanil concentrations were measured by specific radioimmunoassay (12). Heat pain thresholds were measured at the thenar eminence of the dominant hand and reaction times tested on the evening before surgery and 1 h after study drug injection. Heat pain threshold measurements using the Pathtester MPI100 have been reported previously (13–17). Briefly, a contact thermode (6 cm^2) with a microcomputer-controlled Peltier-element is heated at a rate of 0.7°C/s, beginning from a baseline of 40°C. Patients indicated their phasic pain detection thresholds by pressing a button when the heat sensation changed from a warm sensation to a tingling pain. Tonic pain thresholds were determined by allowing the patient to adjust the heat to the tolerance threshold point, experiencing the heat for 30 s and then allowing readjustment. These procedures were explained and practiced on the day before surgery. Evaluation of the pain thresholds was performed according to the Maximum Possible Effect (MPE) method. The maximum possible change was from baseline temperature of 40°C to cutoff at 52°C. The actual heat pain thresholds were converted to percentages of MPE. Statistical evaluation of all variables, as predefined, was performed with the Student's *t*-test. A significance level of $P < 0.05$ was chosen. These data are shown as mean ± SD.

Table 1. Patient Characteristics

Characteristics	Sufentanil and droperidol	Sufentanil and placebo
Knee/hip (*n*)	10/10 (20)	10/10 (20)
Age (yr)	48.4 ± 18	55.5 ± 16
Sex*, female/male	5/15	11/9
Weight (kg)	72.2 ± 13	76.7 ± 14
Height (cm)	168.6 ± 10	170.7 ± 13
Injection site	L2–3: 6 L3–4: 13 L4–5: 1	L2–3: 2 L3–4: 18 L4–5: 0
Chronic analgesics	6	4

Mean values (± SD) are shown.
* $P = 0.053$, Fisher's one-sided test.

Results

Patients' characteristics are shown in Table 1. The demographics of the treatment groups were similar, except for the sex ratio, as women outnumbered men in the group with sufentanil and placebo. The protocols of the 20 patients accrued in each group (10 knee and 10 hip endoprostheses in each group) were fully evaluable. There were no group differences in the duration of and complications during intraoperative epidural anesthesia, which was satisfactory in all cases.

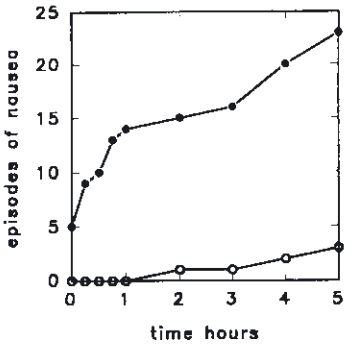

Figure 1. Cumulative incidence of episodes of nausea in 20 patients given sufentanil and droperidol (open circles) or sufentanil and placebo (filled circles) epidurally postoperatively.

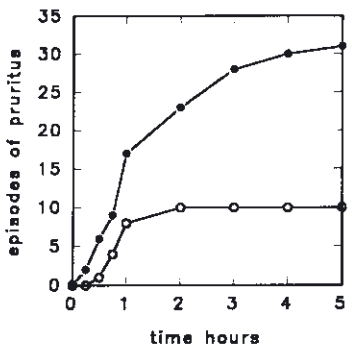

Figure 2. Cumulative incidence of episodes of pruritus in 20 patients given sufentanil and droperidol (open circles) or sufentanil and placebo (filled circles) epidurally postoperatively.

Three patients in the group given sufentanil with droperidol (three episodes) and 12 patients with sufentanil and placebo (23 episodes) developed nausea ($P < 0.007$). No patient with droperidol and two with sufentanil and placebo experienced moderate to severe nausea. The time profile of the prevalence of nausea in both treatment groups is shown in Figure 1. With sufentanil and droperidol no patient had emesis, whereas three patients vomited with sufentanil and placebo (22 episodes) ($P < 0.001$).

Pruritus was reported by six patients in the group given sufentanil and droperidol (10 episodes) and by 11 patients with sufentanil and placebo (31 episodes) ($P < 0.05$). Pruritus was most prominent 1 h after sufentanil and lasted for 1 to 2 h in most patients (Figure 2). The intensity was classified as moderate to severe in one patient with droperidol and in seven with placebo.

Twenty patients with sufentanil and droperidol were considered sedated; in four the sedation was moderate to severe. In those given sufentanil and placebo, 13 patients were sedated, three to a moderate or severe degree. The difference between the two groups was significant ($P < 0.02$). Sedation rapidly increased within the first 15 min and was at a maximum in the first 2 h after study drug injection. The greatest differences in sedation between the two groups was evident from 1 to 4 h.

Four patients had developed shivering before sufentanil with droperidol and two before sufentanil with placebo application. In both groups, shivering abruptly ceased in all patients after study drug injection, but recurred after 6 h in all. One additional patient in each group developed shivering 2 h after the study drugs.

Urinary retention occurred in 14 patients with sufentanil and droperidol and in 10 patients with sufentanil and placebo and usually resolved with an antispasmodic drug (not significant).

Mean arterial pressure decreased from 94.6 ± 1 mm Hg before sufentanil and droperidol to a minimum of 84.3 ± 9 mm Hg 45 min after injection (Figure 3). Seven patients had periods of hypotension. Three patients were given atropine and one received ephedrine. In the sufentanil and placebo group, the mean arterial pressure decreased from 94.3 ± 16 mm Hg before sufentanil to a nadir of 87.7 ± 15 mm Hg 45 min later. Six patients were hypotonic; four received atropine and two ephedrine. The heart rate was 69 ± 14 bpm before sufentanil and droperidol and 71 ± 10 bpm before sufentanil and placebo. In both groups there were no significant changes or differences in heart rates throughout the study. Seven patients with droperidol and eight with placebo had periods of bradycardia (pulse <60 bpm).

Immediately before the injection of study drugs, the mean oxygen saturation was 94.4% ± 3% in the sufentanil and droperidol group and 94.9% ± 2% with sufentanil and placebo. The lowest group O_2-saturation was seen 4 h after sufentanil and droperidol (93% ± 2%) and 5 h after sufentanil and placebo (93% ± 3%) (Figure 4). Saturation below 90% occurred in 13 patients with droperidol (16 episodes) and in seven patients with placebo (14 episodes) ($P < 0.05$ for number of patients). In both groups, over 80% of all desaturation episodes took place in the first hour after sufentanil injection.

Dizziness was reported in four cases with droperidol and in six cases with placebo. No extrapyramidal side effects were seen.

The pain scores before study drugs were 2.1 ± 0.9 in the sufentanil/droperidol group and 2.7 ± 0.8 in the sufentanil/placebo group ($P < 0.05$) (Figure 5). The lowest group pain score with sufentanil and droperidol was attained 30 min postinjection (0.2 ± 0.4), 16 patients being completely without pain (Table 2). The minimum pain score was reached 1 h after sufentanil

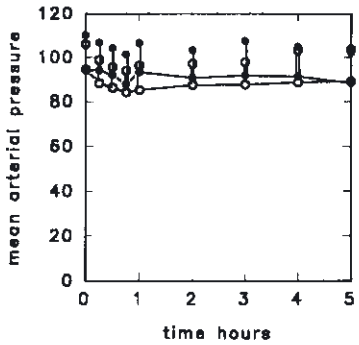

Figure 3. Mean arterial pressure (SD) in 20 patients given sufentanil and droperidol (open circles) or sufentanil and placebo (filled circles) epidurally postoperatively.

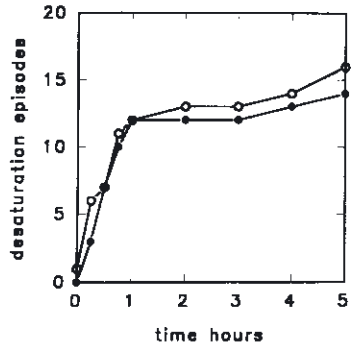

Figure 4. Cumulative incidence of episodes of desaturation (aO_2 <90%) in 20 patients given sufentanil and droperidol (open circles) or sufentanil and placebo (filled circles) epidurally postoperatively.

and placebo, with a mean pain score of 0.05 ± 0.2; all but one patient were completely painfree (Table 2). Group pain scores were consistently higher with droperidol from 1 to 5 h postinjection in patients up to the first add-on analgesia, but this was significant only at 1 h ($P < 0.01$) (Figure 5).

The average time to first additional analgesia was 127 ± 48 min with droperidol and 173 ± 54 min with placebo ($P < 0.02$). In the droperidol group, 19 patients required supplementary analgesia, five of them twice in the 5-h period. With sufentanil and placebo, 17 patients had supplementary analgesics, eight requiring a second and one a third dose.

The mean MPE on phasic pain thresholds in the sufentanil and droperidol group were 41.8% ± 20% preoperatively and 44.6% ± 19% postoperatively (not significant). Respective values in the sufentanil and

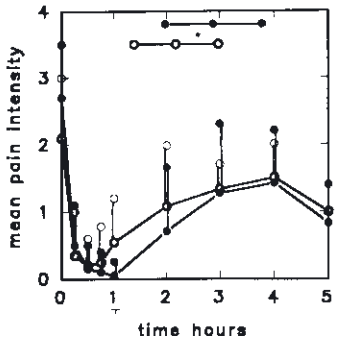

Figure 5. Mean pain scores (SD) (verbal rating scale: 0 = none, 4 = unbearable) in 20 patients given sufentanil and droperidol (open circles) or sufentanil and placebo (filled circles) epidurally. The mean times (SD) to first supplemental analgesia are shown as horizontal bars in the diagram. *$P < 0.05$; †$P < 0.01$.

placebo group were 40.1% ± 18% and 47.4% ± 19% ($P = 0.01$). The MPE on tonic pain thresholds increased significantly with both droperidol, from 37.1% ± 16% preoperatively to 48.8% ± 18% postoperatively ($P < 0.002$), and placebo, from 35.2% ± 14% preoperatively to 48.0% ± 18% postoperatively ($P < 0.0005$). Reaction times showed no relevant changes.

Ten patients with sufentanil and droperidol described analgesia as excellent, nine as good, and one as inadequate. The respective ratings with sufentanil and placebo were nine, nine, and two. Time profiles of the mean plasma sufentanil concentrations are shown in Figure 6. There were no differences in mean group concentrations at any time.

Discussion

The addition of epidural droperidol to epidural sufentanil in the treatment of postoperative pain resulted in a marked reduction in both the incidence and intensity of nausea, emesis, and pruritus. These effects of droperidol lasted throughout the 5-h observation period. After the administration of sufentanil, arterial blood pressure decreased, but this rapid and slight decrease was similar with droperidol and placebo. Sedation was prominent in both treatment groups and was usually minimal. The greater incidence of sedation with droperidol derived mainly from the latter part of the study, where the residual effect of droperidol and the earlier use of supplementary analgesics may have had an additive effect. Oxygen desaturation occurred slightly more often in patients with droperidol. This may be attributable to the greater sedation in these patients. Respiratory depression was short-lasting with

Table 2. Pain Scores up to Time of Supplemental Analgesia After Postoperative Epidural Injection of Sufentanil with Droperidol or Sufentanil with Placebo

	Time (hours postinjection)								
	0[a]	0.25	0.5	0.75	1.0	2.0	3.0	4.0	5.0
Sufentanil and droperidol, pain score									
Patients (*n*) without supplemental analgesia									
0 (No pain)	0	15	16	16	12	4	0	0	0
1	7	3	4	3	5	5	2	1	1
2	4	2	0	1	3	3	1	1	0
3	8	0	0	0	0	1	0	0	0
4 (Maximum pain)	1	0	0	0	0	0	0	0	0
Patients (*n*) with supplemental analgesics	0	0	0	0	0	7	17	18	19
Sufentanil and placebo, pain score									
Patients (*n*) without supplemental analgesia									
0 (No pain)	0	11	17	18	19	10	3	1	1
1	2	7	3	2	1	4	4	2	2
2	4	2	0	0	0	2	3	2	0
3	11	0	0	0	0	1	1	0	0
4 (Maximum pain)	3	0	0	0	0	0	0	0	0
Patients (*n*) with supplemental analgesics	20	0	0	0	0	3	9	15	17

[a] Preinjection, baseline pain score.

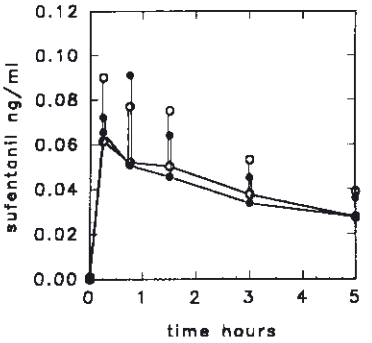

Figure 6. Mean plasma sufentanil concentrations (sn) in 20 patients given sufentanil with droperidol (open circles) or placebo (filled circles) epidurally.

both treatments, usually disappearing by the first hour after epidural injection.

Epidural sufentanil with placebo virtually eliminated all postoperative pain in the first 2 h after administration with a latency of less than 15 min, even though 70% of initial pain scores had been "strong" or "severe." The average reduction of pain severity after 1 h was 98%. This corresponds well with the published data (1,2,18). The combination of sufentanil and droperidol also decreased pain intensity very markedly—91% after 30 min—but the duration of analgesia was significantly shortened. This was demonstrated by a more rapid increase in pain scores and the earlier need for supplemental analgesia. On average, patients with droperidol required supplemental analgesia 46 min earlier than patients with sufentanil and placebo. Most patients requested additional analgesics when their pain score was 2. Patients were equally satisfied with both treatments. This confirms the patients' expectation and acceptance of some residual pain as the normal condition in the postoperative situation, which can be changed by improving patient instruction (19). The difference in the duration of analgesia between the two treatment groups was not due to pharmacokinetic factors, as these were unchanged by the addition of droperidol. The plasma levels seen at the time of maximum analgesic effect were a fraction of those reported for analgesia or antinociception with systemic administration, indicating a predominantly spinal site of action after epidural injection (20–22). This was the rationale for the epidural administration of sufentanil in this study, as well as the greater routine use and acceptance of the epidural route compared to the intrathecal use. Nonetheless, the systemically absorbed sufentanil may also have contributed to the analgesia by a supraspinal action.

The significant increase in both sufentanil groups of postoperative tonic heat pain thresholds, which reflect mainly C-fiber activation, indicates the successful suppression of postoperative nociceptive activation (windup) with the anesthetic and analgesic regimens used. The phasic pain thresholds are mainly mediated via A-δ pathways, which are less implicated in the long-term nociceptive up-regulation than in the referral of acute pain. The significant elevation in the phasic pain

thresholds only in the sufentanil- and placebo-treated patients, at a time when pain scores were significantly lower in this group (1 h after study drug injections), can be taken to confirm the relationship between acute pain blockade and phasic pain threshold measurements.

No neuroleptic-specific side effects were seen in this or the previous study, even though, theoretically, extrapyramidal signs could occur. Perispinal droperidol has been used previously with no histopathologic effects on the spinal cord (23–25).

The results of the current study confirm the significant reduction in excitatory side effects, such as nausea, emesis, and pruritus, of epidural μ agonist opioids by epidural droperidol. In an earlier study these opioid side effects after epidural morphine were reduced markedly by concomitant epidural droperidol, without a clear effect on analgesia (9). To better investigate the possible analgesic interaction between opioids and epidural droperidol, we chose the shorter-acting, more potent and specific μ agonist, sufentanil. The interference with the excitatory and analgesic properties of opioids may be due to several of the receptor affinities of droperidol. These include weak 5-hydroxytryptamine antagonism, α_1 and α_2 (weak) agonism, and the predominant dopamine D2 receptor antagonist properties (26–29). Dopamine pathways play an important role in the emetic response via modulation at the chemoreceptor trigger zone (central effect) and peripheral sensory and motor inputs (29). Spinal descending dopaminergic pathways are involved in nociception and current data seem to suggest that dopaminergic stimulation results in potentiation of antinociception (30–32). This would explain the abbreviated duration of analgesia of sufentanil seen in the current study, when the dopamine antagonist was added. The interaction probably varies with the route of application of the dopamine antagonist and the dose used, as different dopamine receptor populations may be reached spinally and supraspinally and they may have different response characteristics (25,32,33). Droperidol given epidurally will have had both spinal and central effects.

The effect of epidural droperidol on morphine-induced analgesia has not been consistent in past studies. In our own previous study, pain scores were lower with morphine and placebo than with morphine and droperidol, especially in the early phase of the study, but did not quite attain statistical significance (9). The early interaction seen with sufentanil may have been less clearly visible with morphine because of the much longer duration of morphine analgesia compared to sufentanil and the greater interval between pain ratings. The largest previous study reported the potentiation of morphine and buprenorphine analgesia with epidural droperidol in chronic pain patients (23). The selection of a subgroup of chronic pain patients tolerant to opioid analgesia in this uncontrolled, retrospective study may have resulted in demonstration of mechanisms quite different to those relevant in postoperative, opioid-naive patients. Alternatively, epidural droperidol may interact differently with opioids of divergent receptor binding affinities.

In conclusion, the excitatory side effects of epidural sufentanil were significantly diminished by epidural droperidol, but the duration of analgesia was decreased. This decreased duration of analgesia is of little consequence when continuous infusions are used, but must be considered when repeated bolus injections are administered. It remains to be ascertained whether similar interaction occurs with the frequently used oral and parenteral opioid-neuroleptic combinations.

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11. *Article* - Epidural Tramadol

(Wilder-Smith CH, Wilder-Smith OH, Farschtschian M, Naji P. Epidural droperidol reduces the side effects and duration of analgesia of epidural sufentanil. Anesth Analg 1994;79:98-104)

Preoperative adjuvant epidural tramadol: the effect of different doses on postoperative analgesia and pain processing

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Background: Tramadol is an analgesic with combined opioid agonist and monoamine reuptake blocker properties, which may be useful as a perioperative analgesic and antinociceptive adjuvant.

Methods: The dose-dependent effects of adjuvant preoperative epidural tramadol on postoperative analgesia (pain scores and patient-controlled analgesia (PCA) use) and pain processing (heat pain thresholds) were prospectively studied in a double-blind, randomised, placebo-controlled 5-day trial. Forty patients undergoing knee or hip surgery received anaesthesia with epidural lidocaine and epidural tramadol 20, 50 or 100 mg or placebo as a preoperative adjuvant. Postoperative analgesia was by intravenous PCA tramadol in all patients.

Results: Postoperative pain scores were similar in all groups. The time to first PCA use was shorter, the total dose and duration of PCA use greater, and side-effects more common with 20 mg tramadol than with 100 mg or placebo ($P<0.05$). There were no differences in PCA doses required or side-effects between the tramadol 100 mg and placebo treatment groups. Heat pain tolerance thresholds were increased with 100 mg tramadol at 48 h postoperatively compared to baseline and placebo ($P = 0.01$).

Conclusions: Preoperative adjuvant epidural tramadol does not improve postoperative analgesia after lidocaine epidural anaesthesia compared to placebo. Tramadol 20 mg results in anti-analgesia and increased side-effects. While tramadol 100 mg depresses postoperative pain-processing, as measured by heat pain tolerance thresholds, this is not reflected in improved clinical pain measures.

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Tramadol is a dual-action analgesic drug, with predominantly μ-opioid agonist and noradrenaline and serotonin release and reuptake blocker action and an active metabolite (1–4). Clinical studies indicate good analgesic efficacy in the oral, parenteral and epidural applications, although the optimal dosing remains unclear (5–13). Relative to morphine, tramadol has a parenteral potency of 1/6th to 1/10th and an oral potency of approximately 0.4 (5, 6). Tramadol differs from other opioids in its side-effect profile, with little cardiovascular and respiratory depression, as well as low dependency potential (5, 8, 14, 15).

The preoperative application of opioids has in some studies been shown to be more effective than when given later, although these results remain controversial. In positive studies the reductions in postoperative analgesic requirements were generally minor, even though increased supraspinal analgesia after surgery was demonstrated (16–19).

Alpha$_2$-adrenergic agonists, with a similar spinal mode of action as the monoaminergic component of tramadol, have been shown to augment the analgesic action of opioids (20). Thus, the combination of the two associated modes of action of tramadol may be useful in the prevention, as well as treatment, of nociceptive sensitisation and pain.

The aim of this study was to assess the analgesic and antinociceptive potential, as well as the side-effects, of different doses of preoperative adjuvant epidural tramadol.

Methods

Patients

Forty patients (ASA I–III) scheduled for elective knee (total knee replacement or cruciate ligament repair) or hip replacement surgery were included in this prospective, randomised, double-blind, single-centre

trial. The randomisation list was computer generated. Exclusion criteria were age below 20 or above 75 years, ASA (American Society of Anesthesiology) classification greater than III, abnormal haematology or biochemistry variables, diabetes mellitus, neuropathies, major operative procedures or pain syndromes in the last 6 months, regular, daily analgesic use, present operative procedure lasting more than 3 h and intraoperative complications. University of Berne Ethics committee approval was obtained for the study.

Procedures and medications

After informed consent, patients were randomised to receive either placebo (0.9% NaCl) or tramadol (Grünenthal AG, Mitlödi, Switzerland) 20 mg, 50 mg or 100 mg epidurally, all in identical ampoules of 10 ml 20 min preoperatively. Doses of 100 mg and 1–2 mg/kg are commonly used parenterally and have been given in epidural studies (6, 10–13, 21, 22). All patients in the current study received 7.5 mg midazolam p.o. 2 h preoperatively. Before lumbar epidural anaesthesia with lidocaine-CO_2 2% (Sintetica AG, Mendrisio, Switzerland) patients were hydrated with 1000 ml of Ringer's lactate. A 3-ml test-dose of lidocaine-CO_2 was given after localisation of the epidural space using the loss-of-resistance technique and a further 3 ml were given after catheter insertion. The lidocaine dose for intraoperative anaesthesia was calculated according to a clinical formula based on age, weight and number of segments to be blocked (23). The first half of this dose was injected epidurally together with the blinded study medication. The second half of the calculated lidocaine dose was given when the sensory level had regressed to the T10–11 dermatomes. Intraoperative sedation with propofol (infusion 2–5 mg $kg^{-1} h^{-1}$) was routine. Two orthopaedic surgeons performed all operations in standardised fashion. Postoperative analgesia was by i.v. PCA tramadol (PCA = patient-controlled analgesia; Pharmacia Deltec CADD, Dübendorf, Switzerland: 50 mg boli, lock-out time of 15 min) in all study arms and was based on the recommendations of Lehmann et al. (6). A loading bolus of 100 mg tramadol i.v. was given postoperatively at the first report of pain in every study arm. No other analgesics were permitted intra- or postoperatively, except for documented rescue medication with metamizole (1 g i.v. maximum once hourly) or pethidine (100 mg i.v. maximum once hourly). Rescue antiemesis was by metoclopramide 10 mg i.v.

Documentation

Blood pressure and heart rate were measured before and 5 min after epidural injection of the study drugs and then every 15 min intraoperatively until 1 h post operatively. Subsequently, measurements were half-hourly until 4 h postoperatively. Oxygen saturation was monitored postoperatively with a pulse oximeter for the first 4 h.

Pain at rest and during movement (getting out of bed), sedation and nausea were postoperatively elicited from the patient every half-hour until 4 h and then 12-hourly until 96 h by the same research nurse throughout the study using verbal rating scores (VRS) of 0 (none), 1 (slight), 2 (moderate) and 3 (severe). The number of emetic episodes, urinary retention (need for catheterisation) and other adverse events were recorded. All rescue medications and each PCA demand were noted on the special documentation protocols. One research nurse followed all patients from admission to discharge and was in charge of all documentation. Patients were asked to record their overall pain intensity, quality of sleep and intensity of nausea by VRS (0–3) on a special data sheet at the end of each 12-h period until 96 h postoperatively.

Heat pain thresholds

Heat pain detection (phasic) and tolerance (tonic) thresholds were measured on the evening before surgery after adequate instruction and at 30 min, 3 h and 48 h postoperatively. They were measured on the thenar eminence of the dominant hand with the Pathtester MPI100 (Phywe GmbH, Göttingen, Germany) to assess generalised, non-segmental antinociception (24). The Pathtester has been previously described and validated (24). The detection thresholds are measured by asking the patient to press a button as soon as the metal Peltier element attains a temperature that begins to feel painful. The metal element is immediately cooled off. The heating rate is set at 0.7°C/s, beginning at 40°C, with a maximum temperature of 52°C. Heating begins after an acoustic signal, but the time to heating is randomised. The mean of 5 measurements is recorded after 3 test runs. For determination of the heat pain tolerance thresholds, the patient himself adjusts the temperature to the point of just tolerable pain, remains at this temperature for 15 s and then readjusts the temperature to the threshold, if necessary. This method excludes variations in reaction time.

Statistics

Pain and symptom VRS, the time to first PCA demand, the total duration of PCA tramadol usage, PCA tramadol consumption and the total number of adverse events were compared using Kruskall-Wallis ANOVA testing followed by Bonferroni-corrected

Mann-Whitney U-testing. Demographics, heat pain thresholds, haemodynamics and O_2-saturation were compared with two-way ANOVA, followed by Tukey's Honest Significant Difference test. A significance level of $P<0.05$ was chosen.

Results

Forty patients were recruited and all successfully completed the study. There were no significant differences in demographic variables (Table 1).

Intraoperative variables: There were no significant differences in intraoperative variables, including haemodynamics, O_2 saturation or total doses and timing of lidocaine use (Table 1).

Postoperative pain scores: The patients' assessment of pain always corresponded with the pain scores collected by the nurse. Consequently, only the nurse's pain ratings are shown. The time courses of median pain scores at rest and during movement are shown in Fig. 1. There were no significant differences in group median pain scores at rest (Fig. 1a). The pain scores during movement were similar except on the 3rd postoperative day, when scores were significantly greater in the 20 mg tramadol group than in all other groups ($P<0.05$) (Fig. 1b).

Postoperative i.v. PCA tramadol: The time to first demand was significantly shorter and the total dose and the duration of PCA use were significantly greater in the 20 mg than in the 100 mg and placebo groups ($P<0.05$) (Table 2). There were no significant differences between the latter two groups. The difference in postoperative PCA tramadol doses was not apparent in the first 4 h postoperatively, but developed later (Fig. 2, Table 2).

Rescue analgesia: Throughout the entire postoperative period rescue metamizole was given in 9 instances in the 20 mg group, in 7 in the 50 mg and 100 mg groups and in 10 instances in the placebo group (not significant). Pethidine was never required.

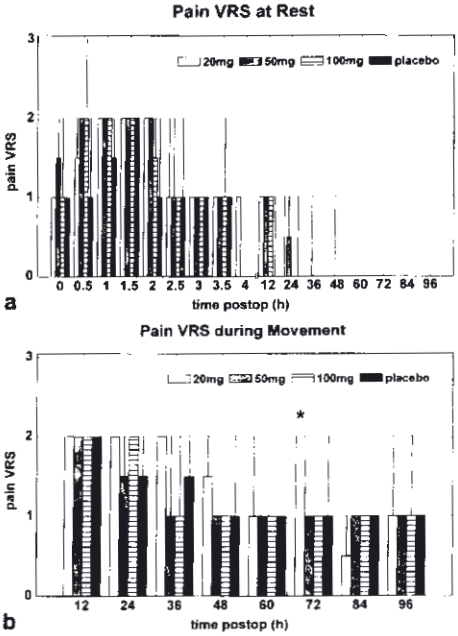

*Fig. 1. Median postoperative pain scores (with interquartile ranges) at rest (1a) and during movement (1b) on a verbal rating scale (VRS): 0=no pain to 3=severe pain. Note the changes of scale in the abscissa after 4 h. * $P<0.05$ 20 mg vs all other groups.*

Heat pain detection thresholds: There were no overall

Table 1

Patient characteristics and intraoperative variables (mean±SD).

	Tramadol 20 mg	Tramadol 50 mg	Tramadol 100 mg	Placebo
N	10	10	10	10
Age (years)	53±20	64±11	62±16	63±14
Sex (m/f)	3/7	4/6	6/4	5/5
Height (cm)	164±8	168±8	168±11	171±10
Weight (kg)	73±13	80±20	71±11	80±16
Hip/knee surgery	6/4	3/7	5/5	6/4
Total lidocaine dose (ml)	33±5	31±5	30±5	31±4
Time between 1st and 2nd lidocaine dose (min)	55.5±17	59.0±14	58.5±16	60.5±7
Epidural site (L1–2/L3–4/L4–5)	0/10/0	3/7/0	2/8/0	2/7/1
Time from study drug to beginning of surgery (min)	38±14	37±9	45±13	35±8
Duration of surgery (min)	78±18	78±18	73±15	77±11

Table 2

Postoperative use of PCA tramadol and additional rescue metamizole (median and total range).

	Tramadol 20 mg	Tramadol 50 mg	Tramadol 100 mg	Placebo
Time to first PCA demand (min)	25 (5–90)*	38 (25–95)	60 (10–125)	68 (15–85)
n PCA demands: first 4 h	8 (6–11)	8 (5–9)	7 (2–16)	8 (4–11)
n PCA demands: 4 h to 4 d	16 (3–27)*	14 (1–20)	7 (2–21)	8 (1–12)
Duration of PCA pump use (h)	72 (24–96)*	60 (24–96)	36 (24–48)	36 (24–48)
n PCA demands: total first 4 d	22 (8–38)*	17 (8–29)	15 (4–32)	16 (5–23)
Total postop PCA tramadol (mg)	1100 (400–1900)*	850 (400–1450)	750 (200–1600)	800 (250–1150)
n with rescue metamizole	9	7	7	10

* $P<0.05$ vs 100 mg and placebo group.

Table 3

Mean changes (±SD) in degrees Celsius of heat pain thresholds from baseline with different doses of epidural tramadol and placebo given preoperatively.

	Pain detection thresholds (change from preoperative baseline)			Pain tolerance thresholds (change from preoperative baseline)		
	30 min	3 h	48 h	30 min	3 h	48 h
20 mg	0.3±1.3	0.0±1.6	0.2±1.4	0.6±1.0	0.7±1.0	0.6±0.8
50 mg	−0.2±0.7	0.0±1.5	0.2±1.0	0.3±1.0	1.0±0.8	0.8±1.2
100 mg	−0.4±1.4	−0.4±1.6	0.1±1.4	0.7±0.6	1.1±1.0	1.2±1.3*
Placebo	−0.8±0.8	0.2±1.3	−0.9±1.4	0.0±0.8	0.5±1.0	0.3±1.0

* $P=0.015$ 100 mg vs placebo.

significant differences at baseline or at any subsequent time between the treatment groups and in no group were there significant changes in thresholds from baseline (ANOVA) (Table 3).

Heat pain tolerance thresholds: There were no overall significant differences in tolerance thresholds between the treatment groups (ANOVA). The effect of time was highly significant. Post hoc testing revealed a significant increase from baseline at 48 h in the 100 mg tramadol group ($P=0.01$). At this time the changes in thresholds from baseline were also significantly different between the 100 mg and placebo treatments ($P=0.015$) (Table 3).

Sedation: Scores were never significantly different between the treatment groups; however, differences at 2.5 h postoperatively just failed to reach significance (Kruskal-Wallis $P=0.06$). Post hoc testing at 2.5 h postoperatively showed significantly greater sedation scores after 20 mg epidural tramadol than with 50 mg or placebo ($P=0.03$ and $P=0.004$, respectively).

Nausea: Median nausea scores were always 0, except during the first postoperative night in the 20 mg and placebo groups (medians=1, ranges=0–2) and at 1.5 h postoperatively in the 50 mg group (median=0.5, range=0–2). There were no significant differences in nausea intensity scores between the treatment groups. Five patients in each group received metoclopramide.

Emesis: In the first 4 h postoperatively vomiting occurred once in every group, except in the 100 mg group, where there were no emetic episodes. In the entire first 4 postoperative days emesis occurred 9 times in the 20 mg group (6 patients), 6 times in the 50 mg group (4 patients), never in the 100 mg group

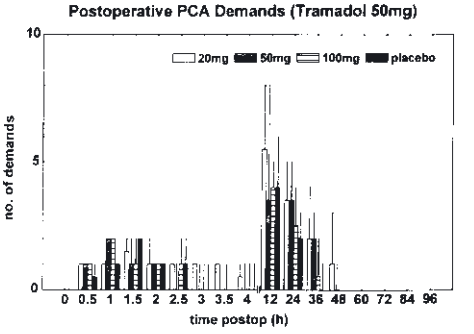

Fig. 2. Median number of postoperative i.v. PCA tramadol demands (bolus=50 mg) in the four treatment groups. Note the change of scale in the abscissa after 4 h.

and twice in the placebo group (2 patients) (100 mg and placebo vs 20 mg $P<0.05$).

Blood pressure and heart rate: Significant hypotension (mean arterial pressure decrease >20%) did not occur in any patient. One patient in the placebo group (at 4 h postoperatively) and another in the 20 mg group (1 h postoperatively) had bradycardia (heart rate <50/min).

Oxygen saturation: Desaturation episodes with SpO_2 below 90% occurred in one patient in each group (20 mg group: 1.5 h postoperatively; 50 mg group: 1.5–2 h postoperatively; 100 mg group: 4 h postoperatively; placebo group: 0.5 and 1.5 h postoperatively). All recovered with oxygen via a transnasal cannula.

Adverse events: The total number of reported adverse events in the first 4 postoperative days was 60 in the 20 mg tramadol group, 49 after 50 mg, 48 after 100 mg and 47 after placebo (20 mg vs others $P<0.05$). The adverse events included sedation, nausea and vomiting, loss of appetite, urinary retention (3, 2, 2, and 4, for 20, 50, 100 mg and placebo groups, respectively), backache, sweating and flushing, dizziness and headache. Pruritus did not occur in any patient, and postoperative shivering was only seen in a single patient in the 20 mg group.

Statistical power: Post hoc testing of statistical power was based on the mean PCA tramadol consumption of the entire group during the first 4 h post surgery ($\alpha=5\%$, $\beta=20\%$, two-tailed). The chosen group size ($n=10$) is able to detect a clinically relevant difference of one-third in PCA tramadol use.

Discussion

Preoperative adjuvant epidural tramadol did not improve clinical postoperative pain control compared to placebo in this study. The preoperative epidural dose of 100 mg was equivalent in analgesic effects and toxicity to placebo, despite raised heat pain tolerance thresholds greater than placebo as a measure of generalised antinociception. Lower doses of epidural tramadol, however, were associated with greater postoperative analgesic consumption, more pain on movement and more side-effects compared to both the placebo and the 100 mg doses. This implies an anti-analgesic effect of lower doses of epidural tramadol.

The failure of preoperative adjuvant tramadol to reduce postoperative pain scores or PCA use compared to placebo may have several explanations. Epidural local anaesthetic alone very effectively reduces intraoperative nociceptive stimulation (16, 17) and postoperative analgesic control with PCA tramadol was excellent. No patient in the placebo group required PCA doses after the second postoperative day and no patient had a median pain score above 0 (i.e. "no pain") after 60 h. Although the sample size was small, the power of the study would have permitted clinically relevant differences in PCA tramadol consumption of one-third to be detected.

The doses and duration of PCA tramadol were greater, and time to first PCA tramadol shorter, in the 20 mg epidural tramadol group than with placebo. This suggests an anti-analgesic or excitatory action of a single low dose of epidural tramadol. In the literature the analgesic effect of single low doses of tramadol in postoperative pain is equivocal, with several studies showing little effect or no difference to placebo (25–27). Inadequate analgesia with increased side-effects has been shown for 25 mg epidural tramadol compared to 50 mg and 75 mg (12). However, with higher or repeated doses, oral parenteral and epidural tramadol has been shown to be an effective analgesic (5, 6, 9, 12, 22), as confirmed by our study.

The reduced analgesia and increased side-effects seen in the 20 mg group compared to placebo are unlikely to be explained by the insignificantly lower mean patient age (Table 1). The difference in time to first PCA demand cannot be explained by variation in the lidocaine block regression because the intervals between the first and second intraoperative lidocaine doses and the durations of operation were very similar in all groups, with the second lidocaine dose being given at the same level of block regression.

Side-effects were more common in the 20 mg group than with placebo or 100 mg. Nausea and vomiting were less prevalent with 100 mg than with placebo. This dose-relationship of the side-effects could be both explained by a direct excitatory effect of low-dose epidural tramadol and by the larger doses of parenteral tramadol the 20 mg group required postoperatively. Other explanations for the dose-related effects of epidural tramadol could include divergent dose-effect reponses of the opioid and the monoaminergic actions of the stereoisomers of tramadol and its metabolites.

Although pain scores or analgesic consumption were similar for the 100 mg tramadol and placebo groups, the postoperative heat pain tolerance thresholds were significantly increased at 48 h in the 100 mg group compared to placebo and baseline. The difficulties associated with the use of clinical pain parameters for measuring dose-response relationships in analgesia have recently been highlighted (28). Pain thresholds were measured in this study, because psychophysical testing provides a measure of changes in perioperative pain-processing (18, 19). The relation-

ship between clinical analgesia (pain scores, PCA use) and changes in pain-processing remains unclear and requires further study. Pain thresholds were determined outside of the operated and anaesthetised dermatomes to measure generalised antinociception, the sum of endogenous and exogenous pharmacologically induced effects. As expected, heat pain tolerance thresholds (C-fibre-mediated pathways) were more affected by opioid antinociception than heat pain detection thresholds (Aδ-pathways) (29). The significantly superior generalised antinociception with 100 mg tramadol compared to placebo is likely to be due to better intraoperative modulation, as postoperative analgesic consumption was similar. Both opioid and monoaminergic mechanisms are known to be involved in descending, inhibitory nociceptive pathways (30). It consequently appears that preoperative epidural tramadol 100 mg had a longlasting postoperative antinociceptive effect, not reflected in the pain scores and analgesic consumption data. This discrepancy has been documented in other studies (19, 31).

We chose the epidural route for preoperative tramadol dosing because of the more sustained effect and because neuraxial application of opioid is considered more effective in suppressing post-nociceptive sensitisation (12, 32). Tramadol is available as a preservative-free formulation and has been applied epidurally in several hundred patients with no evidence of local toxicity (e.g. 10–13, 22, 33). These toxicological data were considered an adequate demonstration of clinical safety by the Ethics Committee at the time of study conception. However, neuropathological studies after epidural tramadol application have to date not been performed and these should be undertaken before general epidural use of tramadol can be propagated.

In conclusion, the preoperative adjuvant epidural use of tramadol did not improve clinical measures of postoperative analgesia. Low-dose tramadol resulted in anti-analgesia and was associated with more postoperative side-effects. Only tramadol 100 mg depressed perioperative pain processing, but this was not reflected in better clinical pain parameters in our study.

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12. *Article* - Intravenous Opioid Agonists vs. Placebo

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Surgical pain is followed not only by spinal sensitization but also by supraspinal antinociception

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Summary

Nociception can produce segmental spinal sensitization or descending supraspinal antinociception. We assessed both types of sensory change after surgery during isoflurane–nitrous oxide anaesthesia with or without fentanyl before nociception. Patients undergoing back surgery received fentanyl 3 μg kg^{-1} ($n = 15$) or placebo ($n = 15$) before anaesthesia in a prospective, randomized, blinded study. Sensation, pain detection and tolerance thresholds to electrical stimulation were measured before operation at the arm, incision and herniated disc dermatomes (HDD) and 1, 2, 4, 6, 24 h and 5 days after operation, together with pain scores and patient-controlled morphine consumption (duration 24 h). For segmental effects, thresholds were normalized to the thresholds at a distant dermatome (arm). Raw pain thresholds were increased after operation (fentanyl > placebo) and were maximal at 4 h (pain tolerance in HDD: fentanyl +5.2 mA (+62.7%), placebo, +3.8 mA (+44.2%); $P < 0.05$ *vs* baseline for both). Normalized sensation thresholds decreased for placebo only (HDD/4 h: placebo, −1.8 (−44.8%), $P < 0.05$; fentanyl, +0.1 (+5.5%) ns). All changes returned to baseline by 24 h except for the placebo group normalized HDD sensation (d5: placebo, −2.4 (−59.7)%, $P < 0.05$; fentanyl −0.1 (−5.5%) ns). Pain scores and morphine consumption were similar. The study demonstrated both supraspinal analgesia and spinal sensitization after surgery. Fentanyl administration before operation augmented the former while decreasing the latter, and hence sensitization, especially if neuropathic, may particularly benefit from pre-emptive analgesia. (*Br. J. Anaesth.* 1996; **76**: 816–821)

Key words

Pain, postoperative. Analgesia, postoperative. Analgesia, pre-emptive. Pain, threshold.

In an editorial discussing pain after surgery, Wall [1] noted, on the basis of animal experimentation, that nociception results in excitatory, segmental changes in central, spinal sensory processing (spinal sensitization). In animal experiments, it was found not only that opioids depress spinal sensitization, but that they were considerably more effective if given before rather than after nociception (pre-emptive analgesia) [2]. The clinical application of these findings has generated considerable debate, with the clinical reality of pre-emptive analgesia remaining controversial and the subject of intensive investigation [3, 4]. In particular, it has proved difficult to demonstrate clinically significant effects on analgesic consumption and clinical pain measures [3, 4].

Groups [5, 6] working on intact animals and with more intense nociceptive stressors described opposing, inhibitory and supraspinal phenomena, such as "stress-induced analgesia (SIA)" or "diffuse noxious inhibitory controls (DNIC)". These groups used nociception that was longer-lasting or more intense, or both, than that of spinal sensitization models (e.g. being forced to swim in hot water *vs* short-lasting electrical stimulation), and found analgesia and hyposensitivity in sensory testing afterwards [7]. Similar sensory inhibition was elicited by stimulation of various brain regions ("stimulation-induced analgesia") [6]. SIA operates via descending, inhibitory encephalinergic, α-adrenergic and NMDA systems [8].

Whether human surgery is associated with spinal sensitization or supraspinal inhibition has not been investigated in detail. Only few studies have examined the effect of pre-emptive analgesia on spinal sensitization; we have found none for SIA or DNIC. Richmond, Bromley and Woolf [9] and Collis and colleagues [10] found that mechanical secondary hyperalgesia was suppressed by pre-emptive morphine, but they did not give absolute thresholds. On a single occasion after operation, Lund, Hansen and Kehlet found an increased electric sensation threshold [11], while electric pain thresholds were decreased (and the nociceptive withdrawal reflex increased) in another study [12]. Both Willer, Bergeret and Gaudy [13] and Peters and colleagues [14] found increased thresholds in small postoperative studies. Thus data on postoperative changes in sensory processing with human surgery are scarce and contradictory.

The aim of this study was to investigate sensory processing after surgery using sensory skin thresholds. In particular, we were interested in

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detecting and differentiating between generalized (e.g. supraspinal inhibition) and segmental (e.g. spinal sensitization) changes in sensory function. We also determined the effect of pre-emptive fentanyl analgesia on changes in sensory processing which might be present after surgery. Finally, we determined if altered sensory processing affects clinical measures of pain (analgesic consumption, pain scores).

Patients and methods

We studied 30 ASA I and II patients, undergoing elective herniated intervertebral disc surgery. The study design was prospective, randomized and double-blind. Institutional review board and Ethics Committee approval were obtained, and all patients gave informed written consent.

Patients were instructed on threshold measurement, pain verbal rating scores (VRS) and use of a patient-controlled analgesia (PCA) pump. They received no premedication on the morning of operation. Before insertion of a venous cannula, pain verbal rating scores (0 = no pain; 10 = worst pain imaginable) for the back and affected leg dermatome and sensation, pain detection and pain tolerance thresholds were determined. Thresholds were obtained using constant skin current stimulation (Digistim, Biometer A/S, Copenhagen/DK; tetanic stimulation at 100 Hz, 0.2 ms square wave pulses) via self-adhesive electrodes 3 cm apart. Measurements were carried out in the middle of the nerve root dermatome most affected by disc prolapse; on the flanks at the height of the back incision (T12–L1 dermatome), ipsilateral and contralateral to the side of the involved nerve root; and the proximal arm contralateral to the involved nerve root (C8–T1). Care was taken not to stimulate major nerves, and measurements were separated by 5 min. The three end-points, measured successively in a run, were the averages of the three runs.

Five minutes before induction of anaesthesia, patients received a blinded short infusion (0.9 % NaCL 100 ml) containing either placebo (placebo group) or fentanyl 3 $\mu g\,kg^{-1}$ (fentanyl group). Anaesthesia was induced with thiopentone 5 $mg\,kg^{-1}$, followed by vecuronium 0.1 $mg\,kg^{-1}$. After tracheal intubation, anaesthesia was maintained with isoflurane and 66 % nitrous oxide in oxygen. No other supplementation was given and the interventions usually lasted less than 1 h.

Thirty minutes after extubation, morphine by patient-controlled analgesia (PCA) was started (loading bolus 60 $\mu g\,kg^{-1}$, PCA bolus 25 $\mu g\,kg^{-1}$; lock-out interval 8 min in recovery room, 15 min on ward; background infusion 15 $\mu g\,kg^{-1}\,h^{-1}$ during the first 2 h in the recovery room). No other analgesics were given. Threshold and VRS measures, as before, and cumulative morphine consumption were assessed 1, 2, 4, 6 and 24 h after extubation. PCA morphine was discontinued 24 h after operation. Threshold and VRS values were obtained 5 days after operation. Observer sedation rating scores (5 = wide awake, 1 = unrousable) were also noted at measurement times.

Based on the data of Lautenbacher and Rollman [15], the study was designed to have the power to detect a difference of 20 % in sensation thresholds. To separate generalized from segmental (spinal) effects on thresholds, normalized (or relative) and raw thresholds were analysed. Thresholds were normalized relative to the arm [9, 10]. Thus normalized thresholds were calculated by dividing para-incisional and affected dermatome threshold values by the respective arm threshold values. All statistical analysis was performed using the software package Statistica for Windows (release 4.5, Statsoft Inc, 2325 East 13th Street, Tulsa, OK 74104, USA). Patient data were compared by unpaired t test. Analysis of thresholds, pain VRS or sedation scores and cumulative morphine consumption was by repeated measures ANCOVA, with the preoperative baseline values acting as covariant. *Post hoc* testing was by Tukey's honest significant difference test. Statistical significance was assumed if $P < 0.05$.

Results

The two groups were comparable (table 1), with similar preoperative (baseline) pain VRS and threshold values. There were no significant differences between groups for back or leg pain VRS, cumulative morphine consumption or observer sedation scores (table 2).

Raw thresholds were increased after operation (table 3, fig. 1). In both groups mainly the 4-h measurements of affected dermatome pain thresholds were increased significantly compared with baseline. Combining all thresholds, the fentanyl group values were significantly higher than the placebo values ($P < 0.02$). Overall, the thresholds at different measurement sites and the sensation, pain detection and pain tolerance thresholds were significantly different ($P < 0.008$ and 0.00001, respectively). Arm site thresholds overall were significantly lower than for the para-incisional site ($P < 0.024$), with no significant difference between para-incisional and affected dermatome thresholds. All three threshold test types differed from each other ($P < 0.0001$). For thresholds overall, values at 24 h and 5 days were generally lower than the preceding postoperative values ($P < 0.0001$). Baseline thresholds significantly affected subsequent values ($P < 0.0001$).

For normalized thresholds taken together (fig. 2), the groups or measurement sites did not differ. Only in the placebo group were sensation thresholds in the affected dermatome significantly lower than baseline at 4 and 6 h and 5 days after operation. Overall, the three threshold test types continued to be different ($P < 0.00001$), and day 5 threshold values together differed from those at 1, 2 and 24 h after operation. For sensation thresholds alone, the values in the placebo group were significantly lower than in the fentanyl group ($P < 0.003$) overall. Baseline values

Table 1 Patient data (mean (SD or range))

	Age (yr)	Weight (kg)	Height (cm)	Sex (M:F)
Placebo	47.8 (24–64)	75.0 (13.4)	171.9 (9.2)	10:5
Fentanyl	41.1 (27–62)	74.3 (14.6)	169.5 (20.6)	12:3

Table 2 Pain, sedation and morphine consumption. VRS = Verbal rating score for leg (L) or back (B) pain; OSS = observer sedation score; morphine = cumulative morphine consumption. Values for VRS and OSS are median (quartile range); cumulative morphine consumption values are mean (SD). BL = Baseline.

	Time after operation						
	BL	1 h	2 h	4 h	6 h	24 h	5 days
VRS/L							
Placebo	0	2	2	1	0	1	0.5
	(0–2.5)	(0–4)	(0–3.5)	(0–4.5)	(0–1.5)	(0–1.5)	(0–2.0)
Fentanyl	1	2	0	0	0	0	2
	(0–2.5)	(1–3.5)	(0–1.5)	(0–1.5)	(0–2.5)	(0–2)	(0–3)
VRS/B							
Placebo	0	5	3	4	2.5	2.5	1
	(0–0.5)	(2.5–5.5)	(2–4)	(2–5)	(0.5–3)	(1–3.5)	(0.5–1)
Fentanyl	0	4	3	3	3	1	1
	(0–1)	(1.5–5.5)	(1.5–4.5)	(1.5–4.5)	(0–4)	(0–2.5)	(0–2)
OSS							
Placebo	5	4	4	5	5	5	5
	(5–5)	(3–4)	(4–5)	(5–5)	(4–5)	(5–5)	(5–5)
Fentanyl	5	4	4	5	5	5	5
	(5–5)	(3–4)	(4–4.5)	(4–5)	(4–5)	(5–5)	(5–5)
Morphine (mg)							
Placebo	0	6.3	9.8	15.3	18.5	33.7	
		(2.3)	(4.1)	(6.2)	(7.2)	(13.5)	
Fentanyl	0	6.4	10.3	16.8	21.1	38.0	
		(1.7)	(5.3)	(9.2)	(12.4)	(29.8)	

Table 3 Absolute threshold values. Values are (mean (SD)) mA, times (except control) are postoperative. C = Incision dermatome contralateral to affected side, I = incision dermatome ipsilateral to affected side, D = dermatome affected most by nerve compression caused by disc prolapse. *$P < 0.05$ *vs* baseline; †$P < 0.05$ *vs* day 5 value. Only the differences at individual times for a given threshold type and dermatome are marked; for other results, see text.

		Time after operation					
	Control	1 h	2 h	4 h	6 h	24 h	5 days
Sensation thresholds							
Arm, placebo	0.8 (0.7)	2.3 (2.4)	2.7 (1.7)	2.0 (1.5)	2.1 (1.4)	2.1 (1.7)	0.8 (1.1)
Arm, fentanyl	1.0 (0.9)	2.1 (1.3)	2.5 (2.2)	1.9 (1.2)	1.7 (0.9)	1.5 (1.3)	0.4 (0.5)
C, placebo	0.8 (0.5)	2.2 (1.5)	2.3 (1.6)	1.9 (1.0)	2.1 (1.3)	2.1 (1.0)	0.7 (0.8)
C, fentanyl	1.1 (0.8)	3.5 (2.4)	3.7 (1.9)	3.0 (1.9)	2.6 (2.0)	2.9 (2.8)	0.5 (0.4)
I, placebo	0.9 (0.5)	2.4 (2.1)	2.2 (1.4)	2.1 (2.1)	2.5 (1.8)	2.2 (1.1)	0.6 (0.5)
I, fentanyl	1.2 (0.8)	2.7 (2.1)	3.0 (1.7)	2.6 (1.5)	2.4 (1.2)	1.7 (1.1)	0.5 (0.4)
D, placebo	1.9 (2.1)	3.7 (2.4)	3.3 (2.7)	3.5 (2.4)	3.3 (2.5)	2.9 (2.7)	1.0 (1.3)
D, fentanyl	1.4 (1.1)	3.2 (2.4)	3.2 (2.1)	3.2 (2.8)	2.5 (1.5)	1.8 (1.4)	0.9 (0.9)
Pain detection thresholds							
Arm, placebo	5.3 (3.5)	6.4 (4.1)	6.6 (4.6)	6.2 (3.5)	5.4 (2.9)	6.3 (3.3)	2.8 (3.7)
Arm, fentanyl	4.9 (3.2)	7.9 (3.5)	8.1 (3.3)	7.0 (3.2)	6.3 (3.4)	5.6 (3.2)	3.6 (3.1)
C, placebo	5.1 (3.7)	7.3 (3.6)	7.7 (3.9)	7.5 (3.3)†	7.4 (3.8)†	7.4 (4.1)†	2.8 (2.9)
C, fentanyl	5.4 (3.1)	9.5 (4.0)	8.3 (3.2)	8.5 (3.4)	7.8 (3.8)	6.8 (4.2)	3.1 (3.5)
I, placebo	5.2 (4.0)	8.4 (5.0)†	7.9 (5.1)†	7.7 (4.9)†	7.6 (4.2)†	8.3 (4.1)†	2.6 (3.3)
I, fentanyl	6.1 (3.1)	8.0 (3.4)	9.0 (3.5)	8.0 (3.3)	8.1 (3.5)	6.2 (3.6)	2.6 (2.2)
D, placebo	5.7 (5.2)	8.0 (5.1)	7.8 (5.1)	8.5 (5.2)†	9.3 (5.2)†	6.9 (4.7)	2.9 (3.5)
D, fentanyl	4.8 (2.8)	8.4 (4.0)	8.0 (3.8)	9.6 (6.2)†‡	7.0 (3.1)	6.6 (3.0)	3.7 (3.0)
Pain tolerance thresholds							
Arm, placebo	9.7 (4.2)	11.6 (5.0)†	10.4 (5.3)	10.6 (4.3)†	10.2 (4.0)†	9.4 (3.7)	5.2 (4.4)*
Arm, fentanyl	8.9 (4.0)	12.6 (3.2)†	13.1 (3.8)†	11.7 (4.4)†	10.4 (5.1)	8.8 (3.8)	5.9 (4.6)
C, placebo	9.6 (5.1)	11.6 (3.8)†	12.2 (4.4)†	12.8 (4.4)†	12.1 (4.8)†	11.1 (4.9)†	5.4 (4.7)
C, fentanyl	9.0 (3.1)	13.9 (4.3)†	13.5 (4.1)†	14.0 (4.4)†*	13.0 (5.4)†	10.1 (5.1)†	5.6 (5.5)
I, placebo	9.3 (4.7)	11.7 (5.7)†	12.5 (5.8)†	11.6 (5.2)†	11.8 (5.0)†	12.1 (4.5)†	4.9 (4.3)
I, fentanyl	9.5 (3.4)	15.0 (5.8)†	13.7 (4.4)†	13.3 (4.3)†	13.6 (3.8)†	9.9 (4.1)	5.7 (4.8)
D, placebo	8.6 (6.0)	11.4 (5.8)†	11.4 (6.0)†	12.4 (6.3)†*	13.2 (6.2)†*	10.4 (5.7)†	5.1 (4.9)
D, fentanyl	8.3 (4.3)	12.6 (5.5)	12.6 (5.1)	13.5 (8.0)†*	11.0 (6.0)	9.6 (4.7)	7.2 (6.3)

influenced normalized thresholds only up to 4 h after operation.

Discussion

In this study, surgery was associated with generalized sensory inhibition and segmental sensitization in the immediate postoperative period. Changes in sensory processing generally returned to baseline within 24 h after operation. Compared with placebo, pre-emptive fentanyl inhibited segmental sensitization, and was accompanied by increased generalized sensory inhibition. These differences between groups were not significantly reflected in clinical measures such as pain scores or morphine consumption in our study, indicating the importance

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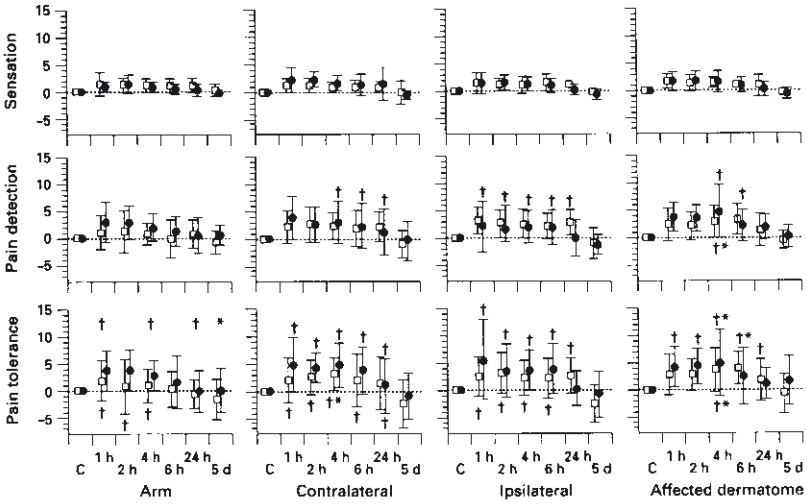

Figure 1 Changes from baseline of raw sensory thresholds (mean, SD mA). The dermatomes tested (X axis) and the types of threshold tests (Y axis) are indicated. *$P < 0.05$ *vs* baseline; †$P < 0.05$ *vs* day 5 value. The significances for the placebo group are marked above the zero line, those for the fentanyl group, below. Only differences at individual times within a given graph are marked (for other results, see text).

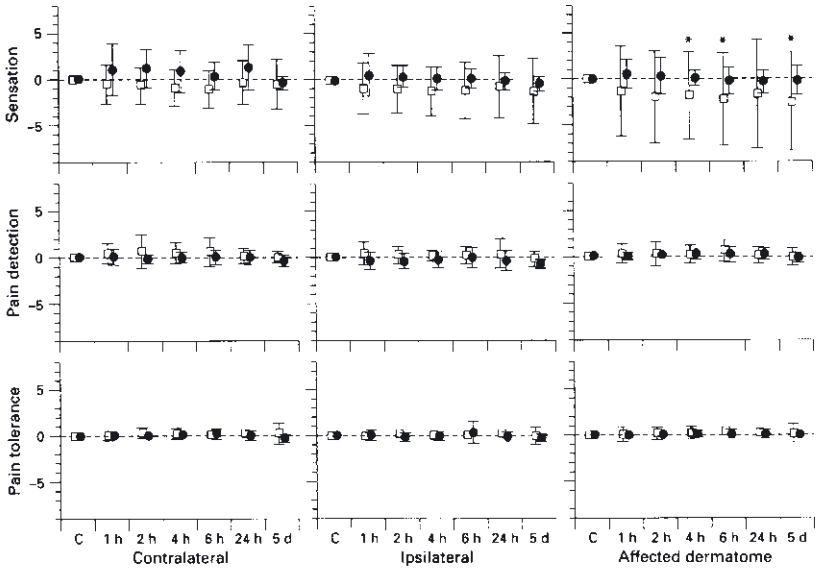

Figure 2 Changes from baseline of normalized sensory thresholds in arbitrary units (mean, SD rations). The dermatomes tested (X axis) and the types of threshold tests (Y axis) are indicated. *$P < 0.05$ *vs* baseline. The significances for the placebo group are marked above the zero line, those for the fentanyl group, below. Only differences at individual times within a given graph are marked (for other results, see text).

of sensory testing in assessing nociception after operation.

Measurement of pain thresholds by cutaneous electrical stimulation is easy to use and well validated [15]. While electrical thresholds do not represent a pure nociceptive activation, but a mixed nerve fibre population response, we consider its use acceptable in the surgical context because surgery also involves

a mixed response. Additionally, use of the more complex equipment necessary for pure nociceptive stimulation (lasers, Peltier elements) is difficult if not impossible on the ward. Possible sensitization by threshold measurements was minimized by spacing the measures, doing only three runs and stopping on just reaching the pain tolerance threshold. In common with other groups [9, 10] we normalized thresholds relative to the arm. Because the arm was far away from the surgical site, it was unlikely to be affected by segmental or spinal sensory changes after operation, while still being subject to any generalized or supraspinal changes, making possible separation of the two types of altered sensory processing.

Extraneous factors which may have influenced thresholds include increased reaction times and analgesic or anaesthetic drugs. In order to decrease the effect of reaction times, electric stimulation was increased very slowly (approximately 0.1 mA s^{-1}). In addition, sedation scores were similar between groups throughout, and were normal by 4 h after operation. Isoflurane in subanaesthetic concentrations has no effect on pain detection thresholds [16]; nitrous oxide may increase pain detection thresholds for up to 30 min after its discontinuation [17]. Opioids such as morphine or fentanyl have no direct effects on sensation or pain detection thresholds [18]. The effects on pain tolerance thresholds are most visible if the stimulus is long or repeated, and are small for tolerance to single pain stimuli [18]. Thus direct drug effects on the thresholds can be expected to have been minimal, particularly with regard to sensation and pain detection thresholds.

Patients titrated themselves to similar pain levels in the groups using PCA morphine. The lack of difference in morphine consumption may primarily result from group size, or because back surgery is only moderately painful, or both. The group size had the statistical power to detect a difference of 50 % in morphine consumption at 24 h between the groups. These results suggest that sensory testing may be more sensitive in the assessment of change after operation than clinical measures such as morphine consumption or pain scores. The relevance of such sensory changes for long-term outcome needs investigation.

We have found no other studies which have systematically investigated sensory thresholds after surgery in humans with regard to spinal sensitization or supraspinal inhibition. Richmond, Bromley and Woolf [9] and Collis and colleagues [10], studying pre-emptive morphine for hysterectomy, found postoperative differential (i.e. forearm–abdomen) pain detection thresholds to mechanical stimulation to be smaller in the pre-emptive group, suggesting less spinal sensitization. There was no difference in sensation thresholds. No preoperative measures were given, however, making further interpretation difficult. The absence of threshold values in a dermatome distant to the surgical site precludes conclusions about the presence or absence of generalized sensory inhibition. The mainly raised thresholds in the studies of Lund, Hansen and Kehlet [11], Dahl and colleagues [12], Willer, Bergeret and Gaudy [13] and Peters and colleagues [14] have already been mentioned. Their results are difficult to compare with ours, as they involved different times, sites and methods.

The increased sensory thresholds after operation demonstrated in our study are likely to be the result of descending central inhibitory controls elicited by the nociception of surgery (e.g. SIA or DNIC [5–8]. Sensory inhibition in our study was generalized and detectable up to 24 h after operation. DNIC operates on convergent neurones and generally fades shortly after the conditioning stimulus [19], making it a less likely mechanism in this case than SIA. SIA is supported further by the fact that while DNIC is depressed by opioids [20], SIA has been described as being augmented by opioid supplementation [21, 22]. However, SIA mechanisms are complex, involving both opioid and non-opioid pathways, possibly mutually antagonistic [23], and a final understanding must await more complete elucidation of this phenomenon. The only possible alternative explanation could be the level adaptation theory, which postulates that pain thresholds change because of resetting of the reference point for pain thresholds [14]. This theory is unlikely to explain the shift in *sensation* thresholds also seen in our study, but definite differentiation would depend on measurement of the nociceptive withdrawal reflex [14] not performed in our study. It should however be remembered that the withdrawal reflex is affected by changes both in the sensory and motor system. Segmental spinal sensitization caused by nociception is also well described in the literature for animal models [2, 3]. Studies confirming spinal sensitization after nociception in human volunteers have now been performed [24], but formal clinical studies are still lacking, as are studies of the long-term implications of such changes for outcome after surgery.

The fentanyl supplemented group showed more supraspinal antinociception after operation than the placebo group. This would suggest that, as shown experimentally [21, 22], opioids act synergistically with descending inhibitory systems, providing another rationale for pre-emptive analgesia. Opioids are effective at preventing and treating spinal sensitization, particularly of the nociceptive system [4], as confirmed by our study. The fentanyl group showed no segmental sensitization; in the placebo group it was visible only for the somatosensory system. Expression of nociceptive system sensitization in the placebo group may have been suppressed by morphine analgesia in the context of only moderately nociceptive surgery, leaving only somatosensory sensitization visible [25]. This possibility needs further study using more painful surgical interventions and larger patient groups. In the placebo group, segmental sensitization was still present compared with the fentanyl group in the affected dermatome 5 days after operation, at a time when all other sensory changes had reverted to normal. This suggests that under special circumstances (e.g. the presence before surgery of neuropathic pain or sensitization associated with nerve damage), changes in sensory processing can persist long-term with poorly blocked pre- or intraoperative

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nociception, as also suggested by the amputation studies of Bach, Noreng and Tjellden [26]. Further studies are needed to confirm this.

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13. *Article* - Intravenous Opioid Agonists vs. NMDA Antagonists

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Sensory Changes and Pain After Abdominal Hysterectomy: A Comparison of Anesthetic Supplementation with Fentanyl Versus Magnesium or Ketamine

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Drugs interacting with opioid or *N*-methyl-D-aspartate (NMDA) receptors may have differing effects on postsurgical sensory changes, such as central inhibition or spinal excitation. We compared the effect of supplementing isoflurane/N_2O/O_2 anesthesia with an opioid agonist (fentanyl [n = 15]) or two drugs inhibiting the NMDA system differently (magnesium, ketamine [n = 15 in each group]) on sensory changes after abdominal hysterectomy. Electric sensation, pain detection, and pain tolerance thresholds were determined (preoperatively and 1, 4, 24 h, and 5 days postoperatively) in arm, thoracic, incision, and leg dermatomes together with pain scores and cumulative morphine consumption. Thresholds relative to the arm were derived to unmask segmental sensory changes hidden by generalized changes. Absolute thresholds were increased 1–24 h, returning to baseline on Day 5, without overall differences among drugs. Fentanyl thresholds were lower 1 h and higher 5 days postoperatively compared with magnesium and ketamine; thresholds were lower at 24 h for magnesium versus ketamine. Relative thresholds increased compared with baseline only with fentanyl (1–4 h); none decreased. Pain scores and morphine consumption were similar. Thus, all adjuvants suppressed spinal sensitization after surgery. Fentanyl showed the most, and magnesium the least, central sensory inhibition up to 5 days postoperatively, with different patterns of inhibition directly postsurgery versus later. Differences in sensory processing were not reflected in clinical measures. **Implications:** We studied the effects on postsurgical sensory processing of general anesthesia supplemented by drugs affecting opioid or *N*-methyl-D-aspartate receptors using sensory thresholds. Generalized central sensory inhibition, differently affected by the drugs, predominated after surgery. All drugs suppressed spinal excitation. Clinical pain measures did not reflect sensory change.

(Anesth Analg 1998;86:95–101)

Nociception alters sensory processing via peripheral and central mechanisms (1,2). Animal models of central sensory change after nociception demonstrate excitation as well as inhibition (3,4). Spinal excitation depends on activation of dorsal horn *N*-methyl-D-aspartate (NMDA) receptors by excitatory amino acid transmitters (3). Opioids depress spinal excitation by inhibiting the initial wide dynamic range (WDR) dorsal horn neuron response to incoming nociceptive C-fiber volleys, without directly affecting neuron hyperexcitability or wind-up (5). NMDA receptor blockers directly inhibit wind-up and hyperexcitability in WDR dorsal horn neurons without affecting the initial WDR response to incoming C-fiber volleys (3).

Central inhibition has been described in at least two variants, stress-induced analgesia (SIA) or diffuse noxious inhibitory controls (DNIC) (4,6–8). Central inhibition is generalized, opposes spinal hyperexcitability, and involves descending control originating from supraspinal structures, such as the midline periaqueductal grey and the locus coeruleus, via either the spinal dorsolateral funiculus or more diffuse propriospinal connections (4,6–8). Longer-lasting SIA comprises neural and humoral opioid, monoaminergic, and nonopioid mechanisms, with the latter including NMDA receptors (6). In animals, opioid agonists augment opioid SIA induced by moderate stressors (e.g., warm water swim). NMDA receptor antagonists decrease

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nonopioid SIA associated with severe stressors (e.g., cold water swim) (4,6). DNIC acts on convergent neurons, fades with the conditioning stimulus, and is thus shorter-lasting (7,8). It is inhibited by morphine; interactions with NMDA antagonists have not been described (7,8).

According to animal studies, opioid agonists and NMDA antagonists may thus exhibit similar effects on spinal sensory excitation but opposing effects on aspects of central sensory inhibition (3–8) after nociception. In a recent human study (9) of sensory changes after surgery, adjuvant opioids suppressed spinal excitation and augmented central inhibition compared with isoflurane/nitrous oxide/oxygen anesthesia alone, as predicted by animal models. The effects on postsurgical sensory changes of substances acting on the NMDA as opposed to opioid receptor systems have not been studied.

We aimed to study the effect of a μ-opioid agonist (fentanyl) or two different NMDA antagonists (ketamine, magnesium) as adjuvants to general anesthesia on the state of sensory processing after surgical nociception. A major goal was to investigate whether these substances have similar or opposing effects on postsurgical central inhibition compared with spinal excitation.

Methods

After local institutional review board/ethics committee approval and informed patient consent, 45 ASA physical status I or II patients undergoing elective abdominal hysterectomy via Pfannenstiel incision were prospectively randomized to receive either fentanyl, ketamine, or magnesium (n = 15 per group) anesthetic supplementation. Statistical power calculations (α = 5%, β = 10%) based on a previous study (9) suggested that a group size of 15 should detect differences in pain tolerance thresholds of one-third, and in 24-h morphine consumption of one-half. Exclusion criteria included systemic hypertension, epilepsy, chronic magnesium, hypnotic or analgesic use, and diseases predisposing to altered sensation (e.g., diabetes mellitus, neuropathies).

During the anesthesia interview, patients were instructed about threshold measurement, pain intensity verbal rating scores (VRS; 0 = no pain, 10 = worst pain imaginable) and use of a patient-controlled analgesia (PCA) pump. No premedication was given on the morning before the operation. In the induction room, before the insertion of venous catheters, baseline thresholds were measured by an observer who, like the patient, was blinded to the adjuvant drug used. The same observer performed all measures. Anesthesia was conducted unblinded by an anesthetist not involved in the study or postoperative patient care.

Thresholds were measured using electric constant current skin stimulation (Digistim®; Biometer A/S, Copenhagen, Denmark; tetanic stimulation at 100 Hz, 0.2-ms square waves, self-adhesive electrodes 3 cm apart) on the dominant upper arm (C7 dermatome), the lateral breast fold (T4), 10 cm lateral to the Pfannenstiel incision (T12), and just above the patella (L3). We avoided stimulating major nerves or muscle bundles. The three thresholds—sensation (stimulation just felt), pain detection (stimulation just becomes painful; "first pain" via Aδ-fibers), and pain tolerance (painfulness of stimulation just becomes intolerable; "second pain" via C-fibers) (10)—were measured as the average of three serial assessments within 30 min, separated by at least 5 min.

Three minutes before anesthesia induction, patients received either 1.5 μg/kg fentanyl, 0.5 mg/kg ketamine, or 20 mg/kg magnesium sulfate as a slow (60 s) intravenous (IV) injection. Anesthesia was induced with 5 mg/kg of thiopental, followed by 0.1 mg/kg vecuronium IV. After tracheal intubation, anesthesia was maintained with isoflurane in oxygen/nitrous oxide (1:2). Five minutes before skin incision, either 0.75 μg/kg fentanyl, 0.25 mg/kg ketamine, or 10 mg/kg magnesium sulfate was injected and subsequently repeated at 30-min intervals. The final dose was given approximately 45 min before the end of surgery. Dropout was for operations lasting longer than 2 h or for unsatisfactory anesthesia (hemodynamic values >20% of baseline for >5 min).

Morphine PCA was started 30 min postextubation in the recovery room (loading bolus 40 μg/kg, PCA bolus 25 μg/kg; lockout 5 min, background infusion 15 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Threshold measures, pain VRS, cumulative morphine consumption, and an observer sedation rating score (1 = unrousable, 2 = deeply sedated, 3 = moderate sedation, 4 = minor sedation, 5 = wide awake) were obtained at 1, 4, and 24 h postextubation. PCA morphine was discontinued 24 h postoperatively, and analgesia on the ward continued with *per os* diclofenac. Threshold and pain VRS values were reassessed 5 days postoperatively.

Apart from absolute sensory thresholds, which predominantly reflect generalized sensory inhibition, we also analyzed derived relative (or normalized) thresholds to unmask the weaker segmental effects expected from spinal excitation, as described previously (9). Relative thresholds were calculated by dividing thoracic, incision, or leg threshold values by respective arm threshold values. We chose the arm (C7 dermatome), far from the operation site, and thus was unlikely to be affected by lower thoracic to sacral stimulation with hysterectomy, as the reference site predominantly reflecting generalized sensory changes.

Statistical analysis was performed using Statistica for Windows (version 4.5; Statsoft Inc., Tulsa, OK).

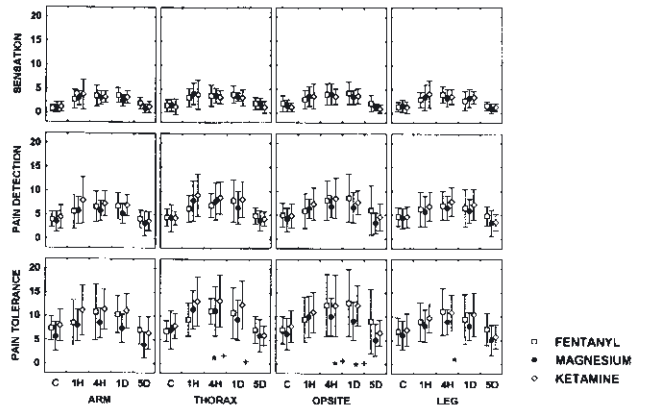

Figure 1. Absolute sensory thresholds (means ± SD). The dermatomes tested are marked below the x axis; the types of thresholds tests are next to the y axis. *Significant versus baseline for fentanyl. +Significant versus baseline for ketamine. Only the threshold differences that are statistically significant for all three factors and time (i.e., drug × site × test × time) are marked; for other results, see text.

Demographic data, cumulative morphine consumption, and thresholds were analyzed by using one-way, repeated-measures two-way, and repeated-measures four-way analysis of variance (fixed effects, three factors: drug [fentanyl, magnesium, ketamine], site [arm, thorax, incision, leg], test [sensation, pain detection, pain tolerance]), respectively. *Post hoc* testing was performed by using Tukey's honest significant difference test. Pain and sedation scores were analyzed by using Kruskal-Wallis analysis of variance and Bonferroni-corrected Mann-Whitney *U*-testing. Statistical significance was set at $P < 0.05$.

Results

All patients completed the study without problems. The fentanyl, magnesium, and ketamine groups were similar for age (48 ± 8, 47 ± 6, and 47 ± 8 yr, respectively [means ± SD]), height (161 ± 6, 162 ± 7, and 158 ± 6 cm, respectively), weight (62 ± 10, 70 ± 9, and 63 ± 9 kg, respectively), and baseline thresholds (Figure 1). Pain intensity VRS, cumulative PCA morphine consumption, and observer sedation scores never differed among groups (Table 1), with pain VRS differences on Day 5 just failing to reach significance ($P = 0.054$).

The overall courses of the absolute thresholds were similar for the drug groups (Figure 1), differing with test types and time ($P < 0.000001$). Thresholds were increased compared with baseline 1–24 h postoperatively, taken together (time), for drug groups (drug × time; $P < 0.000001$), test types (test × time; $P = 0.000003$), or measurement sites (site × time; $P = 0.03$). Thresholds were highest at 4 h, returning to baseline on Day 5. Thoracic and incision thresholds were always similar. Arm thresholds were lower than thoracic thresholds at 1 h and lower than incision thresholds at 4 and 24 h. Leg thresholds were lower than incision thresholds at 24 h (site × time). At 1 h, fentanyl thresholds were lower, and at 5 days they were higher, than for ketamine or magnesium (drug × time). At 24 h, ketamine thresholds were higher than those for magnesium.

In all three groups (drug × test × time), pain detection and tolerance thresholds remain increased compared with baseline ($P < 0.001$) from 1 to 24 h, with the exception of pain detection in the fentanyl group, which was unchanged at 1 h. Sensation thresholds were increased for ketamine at 24 h, for fentanyl at 4–24 h, and for magnesium at 1–4 h. Magnesium pain tolerance thresholds were lower than fentanyl at 5 days and lower than ketamine at 4–24 h. Considering measurement site (site × test × time), pain detection and tolerance thresholds were increased compared with baseline from 1 to 24 h at the thorax and incision sites. Sensation thresholds never changed in the arm and thorax (incision increased at 4–24 h, leg increased at 1–4 h). Leg pain tolerance thresholds were increased at 1–24 h (detection 1–4 h) and were similarly increased for the arm, except at 1 h. At 24 h, incision dermatome pain tolerance thresholds were higher than those for the arm or leg. For all drug groups (drug × site × time), thoracic and incision thresholds were increased versus control at 1–24 h, with the exception of fentanyl, which was unchanged at 1 h, and magnesium/thorax, which was unchanged at 24 h. Arm thresholds remained unchanged with magnesium but were increased at 4–24 h in the fentanyl and ketamine groups. Leg thresholds were increased in all groups at 4 h (ketamine 1–24 h). For

Table 1. Postoperative Pain, Sedation, and Morphine Consumption

	1 h	4 h	24 h	5 days
Pain intensity VRS[a]				
Fentanyl	5 (4–8)	4 (1–5)	1 (0–3)	0 (0–0)
Magnesium	6 (3–8)	3 (3–6)	1 (0–2)	0 (0–0)
Ketamine	5 (5–7)	4 (3–5)	2 (1–3)	1 (0–2)
Cumulative morphine use (mg)[b]				
Fentanyl	5.5 (0.2)	16.9 (0.3)	60.9 (0.9)	—
Magnesium	6.5 (0.2)	15.2 (0.4)	54.2 (1.2)	—
Ketamine	5.7 (1.5)	14.9 (2.7)	55.7 (12.4)	—
Observer sedation score[a]				
Fentanyl	4 (3–4)	4 (3–5)	5 (5–5)	5 (5–5)
Magnesium	3 (2–3)	3 (3–4)	5 (5–5)	5 (5–5)
Ketamine	3 (2–4)	3 (2–4)	5 (4–5)	5 (5–5)

There are no statistically significant differences.
[a] Values are median (interquartile range).
[b] Values are means (SD).

fentanyl at 24 h, leg thresholds were lower than incision thresholds. Significant differences for all three factors and time (i.e., drug × site × test × time) are shown in Figure 1.

For the overall course of the relative thresholds (Table 2), there were no differences among drug groups, tests, or sites, with the difference between fentanyl and ketamine just failing to reach significance ($P = 0.051$). At 1 and 4 h postoperatively, fentanyl relative thresholds were increased compared with baseline and higher than those for ketamine and magnesium (drug × time; $P = 0.00006$). At no time were relative thresholds decreased compared with baseline. There were no significant differences for all three factors and time (drug × site ×test × time) (Figure 2).

Discussion

Neither patients receiving fentanyl nor those receiving ketamine or magnesium revealed evidence of segmental (spinal) hyperexcitability in this study. Regardless of the type of anesthetic supplementation, all patients show generalized (central) inhibition greatest at the site of surgery as the predominant change in sensory processing up to 24 hours postoperatively. Fentanyl patients had the least generalized inhibition just after surgery, accompanied by significant segmental inhibition not present in the other groups. From four hours postsurgery onward, magnesium-supplemented patients exhibited less generalized sensory inhibition than those in the fentanyl or ketamine groups. Five days postsurgery, patients in the ketamine and magnesium groups had lower thresholds than those in the fentanyl group, long after pharmacological actions of the drugs had worn off. These sensory differences were not reflected in clinical pain measures.

The results emphasize the complexity of postsurgical sensory changes and their interactions with analgesic and anesthetic drugs in the intact human. They demonstrate the difficulty of extrapolating results from (frequently nonintact) animal experiments to the clinical situation. All three drugs suppress spinal hypersensitivity. Animal data suggesting interference with SIA by drugs antagonizing the NMDA receptor system are supported by the greater generalized sensory inhibition up to five days postsurgery in the fentanyl group. The differences between ketamine and magnesium may stem from differing effects on non-NMDA systems. Just postoperatively, there is evidence of multisegmental spinal sensory inhibition accompanied by less generalized inhibition in the fentanyl group. The lesser generalized inhibition might be due to inhibition of DNIC-type mechanisms by fentanyl (8), with the spinal inhibition involving direct spinal effects of fentanyl, which are well described in the literature but were not observed in this form in our previous study (9). Conclusive investigation of DNIC depends on measurement of nociceptive flexion reflexes (8), which was not performed in this study. In the absence of direct measures of intraoperative (and postoperative) nociception, it cannot be determined whether the postoperative sensory differences resulted from differing direct perioperative antinociception or from modulation of reactive sensory changes. Neither the relationships among sensory inhibition and nociception and its sequelae, nor their effects on clinical outcomes, are known.

The lack of clinical effects may be the result of a relatively small sample size or too large a background infusion of morphine. *Post hoc* power analysis ($\alpha = 5\%$, $\beta = 10\%$) shows that the study sample size could detect clinically relevant differences of 20% in 24-hour morphine consumption. The background morphine infusion rate was low (0.9 mg/h for a 60-kg patient), providing only approximately one third of total morphine at 24 hours. Virtually all patients demanded a minimum of one bolus per hour in the first 12 hours,

Table 2. Relative Sensory Thresholds

	Baseline	1 h	4 h	1 day	5 days
Sensation					
Thorax					
Fentanyl	4.3 ± 8.7	3.5 ± 8.2	2.5 ± 5.4	1.3 ± 1.0	1.2 ± 0.9
Magnesium	3.5 ± 7.9	1.6 ± 1.5	1.9 ± 2.2	1.7 ± 1.2	8.4 ± 11.9
Ketamine	2.2 ± 3.1	1.1 ± 0.6	1.1 ± 0.6	1.3 ± 1.4	1.0 ± 0.3
Incision					
Fentanyl	6.6 ± 11.8	3.2 ± 6.8	2.3 ± 3.2	1.3 ± 0.9	2.9 ± 3.8
Magnesium	2.8 ± 3.4	1.4 ± 1.4	1.9 ± 1.8	1.8 ± 2.0	6.5 ± 8.2
Ketamine	2.1 ± 2.8	2.0 ± 2.7	1.2 ± 0.7	1.3 ± 1.1	2.1 ± 3.4
Leg					
Fentanyl	4.5 ± 7.4	3.6 ± 9.1	3.9 ± 9.0	0.8 ± 0.5	0.9 ± 0.7
Magnesium	2.1 ± 1.5	1.3 ± 1.4	1.1 ± 0.5	1.6 ± 1.6	7.6 ± 13.1
Ketamine	1.5 ± 1.8	2.3 ± 3.9	1.1 ± 0.6	1.3 ± 1.2	3.8 ± 5.9
Pain detection					
Thorax					
Fentanyl	1.2 ± 0.4	6.4 ± 20.4	4.2 ± 12.1	1.3 ± 0.6	1.4 ± 0.8
Magnesium	1.4 ± 0.7	1.5 ± 0.8	1.4 ± 0.6	1.3 ± 0.5	2.5 ± 3.9
Ketamine	1.2 ± 0.5	1.4 ± 0.7	1.3 ± 0.5	1.3 ± 0.7	1.5 ± 1.3
Incision					
Fentanyl	1.4 ± 0.6	6.3 ± 20.4	5.1 ± 15.2	1.3 ± 0.6	1.6 ± 1.4
Magnesium	1.3 ± 0.6	1.3 ± 0.8	1.2 ± 0.4	1.4 ± 0.8	3.2 ± 4.9
Ketamine	1.3 ± 0.7	1.2 ± 1.1	1.2 ± 0.3	1.1 ± 0.3	1.3 ± 0.6
Leg					
Fentanyl	1.2 ± 0.3	4.9 ± 15.0	5.4 ± 17.3	1.0 ± 0.5	1.4 ± 1.0
Magnesium	1.6 ± 1.2	1.1 ± 0.7	1.2 ± 0.4	1.2 ± 0.4	3.5 ± 7.3
Ketamine	1.1 ± 0.4	1.1 ± 0.8	1.1 ± 0.3	1.1 ± 0.4	1.0 ± 0.5
Pain tolerance					
Thorax					
Fentanyl	1.0 ± 0.5	7.7 ± 25.5	10.3 ± 35.9	1.1 ± 0.5	1.1 ± 0.6
Magnesium	1.4 ± 0.8	1.5 ± 0.4	1.3 ± 0.5	1.3 ± 0.3	1.9 ± 0.7
Ketamine	1.2 ± 0.7	1.3 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	1.0 ± 0.3
Incision					
Fentanyl	1.1 ± 0.5	7.6 ± 25.3	4.3 ± 12.1	1.3 ± 0.6	1.4 ± 1.0
Magnesium	1.2 ± 0.5	1.5 ± 1.2	1.2 ± 0.3	1.2 ± 0.5	1.8 ± 1.2
Ketamine	1.1 ± 0.5	1.2 ± 1.0	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3
Leg					
Fentanyl	1.0 ± 0.2	7.5 ± 25.3	8.9 ± 30.7	0.9 ± 0.3	1.1 ± 0.5
Magnesium	1.2 ± 0.6	1.1 ± 0.4	1.1 ± 0.4	1.2 ± 0.4	1.9 ± 2.1
Ketamine	0.9 ± 0.3	1.0 ± 0.5	1.0 ± 0.2	0.9 ± 0.2	0.9 ± 0.3

Relative (normalized to arm) sensory thresholds (means ± SD) in arbitrary units (ratios).
There are no statistically significant differences for all three factors and time (i.e., drug × site × test × time); for other results, see text.

which suggests that sufficient pain remained for treatment by PCA boli. We did not measure pain during movement, which might be more sensitive to altered sensory processing, although this is speculative. However, it should be noted that the many studies performed to investigate preemptive analgesia have shown the difficulty of demonstrating clinically relevant postoperative effects after analgesic supplementation of anesthesia. This applies not only to fentanyl and ketamine (e.g., Reference 11) but also to magnesium supplementation (12, 13).

Having previously demonstrated spinal excitation after unsupplemented isoflurane/nitrous oxide anesthesia and its suppression by fentanyl supplementation (9), we did not include a placebo group in the present study, using fentanyl supplementation as the standard comparison group, in accordance with typical clinical practice. Fentanyl (μ-opioid receptor agonist), ketamine [noncompetitive NMDA receptor blocker binding at the phencyclidine site of the NMDA ionophore (14)], and magnesium [physiological blocker of NMDA calcium ionophore (15)] all reduce postnociceptive spinal excitation in animal models (3,5,16). Neither ketamine (σ receptor agonism) nor magnesium (generalized calcium antagonism) can be considered pure NMDA antagonists, and both significantly affect the central nervous system (and thus anesthesia) by mechanisms not involving NMDA receptors. Isoflurane and nitrous oxide produce less depression of spinal excitation than opioids or ketamine in animal models (17), not sufficient to suppress sensitization in the clinical surgical context (9).

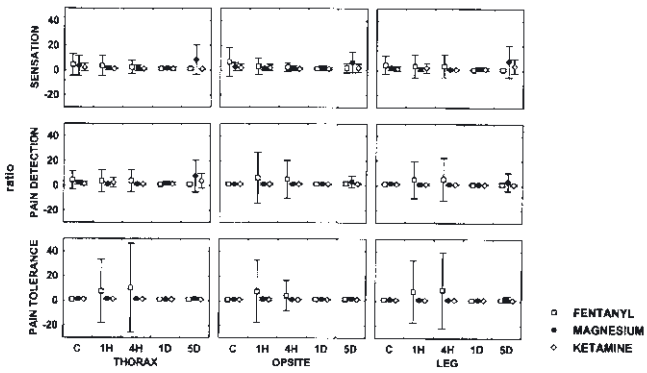

Figure 2. Relative sensory thresholds in arbitrary units (means ± SD). The dermatomes tested are marked below the x axis; the types of thresholds tests are next to the y axis. There were no statistically significant relative threshold differences for all three factors and time (i.e., drug × site × test × time); for other results, see text.

Dosing schemes for fentanyl and ketamine were chosen to correspond to clinical practice. The schemes are comparably analgesic clinically (trough plasma concentrations) based on pharmacokinetic modeling performed by using IVA-SIM [J. Schüttler, S. Kloos, Department of Anaesthesiology, University of Bonn, Bonn, Germany]: fentanyl approximately 0.8 ng/mL, ketamine approximately 0.4 μg/mL) (18,19). Magnesium doses were based on clinical practice in gynecology and anesthesia (20) and significantly increase cerebrospinal fluid concentrations (21) to orders of magnitude depressing electrophysiological NMDA receptor activation *in vivo* (22).

The interpatient threshold variability of our study corresponds with that of other studies (10). Threshold variability was reduced by standardizing instructions, avoiding sensitization (only three well spaced measures, stopping on reaching pain tolerance, no difference between first and last measures), and minimizing reaction time effects (slowly ramped current [approximately 0.1 mA/s]; the similar sedation scores returned to baseline by 4 h). Like surgery, transcutaneous electrical stimulation, simple and frequently used in pain research, results in mixed nerve fiber population activation. Because nonnociceptive surgical inputs also contribute to spinal sensitization (23), this offsets the disadvantage of electrical stimulation not being purely nociceptive.

Anesthetic drug hangover could have influenced thresholds immediately postoperatively. However, increasing thresholds from one to four hours postoperatively make this unlikely. Pain detection thresholds are unaffected by subanesthetic isoflurane concentrations; they may remain increased up to 30 minutes after nitrous oxide (24). Ketamine increases pain tolerance thresholds, particularly for temporal summation, as do opioids (25,26). Opioids have little effect on pain detection and no effect on sensation thresholds (26,27). We found no studies of the effects of magnesium on sensory thresholds. Threshold measures may also have been affected by morphine, another opioid, for analgesia—obligatory for obvious ethical reasons. However, because generalized sensory inhibition affected all thresholds significantly, including sensation and pain detection generally unaffected by opioids, sensory inhibition during the first 24 hours is unlikely to be explained by morphine alone, which suggests the involvement of central mechanisms, such as SIA or DNIC.

Morphine analgesia might have suppressed spinal sensitization. However, a previous study involving intervertebral disc surgery (9) reported spinal sensitization under comparable morphine analgesia. Similar degrees of sensitization should therefore have been detectable in the present study involving abdominal surgery, which is more painful than back surgery (morphine use 56.9 ± 12.8 vs 38.1 ± 25.5 mg/d; $P < 0.05$). Moreover, placebo group segmental excitation in the previous study increased as morphine PCA continued, and in the present study, initial segmental inhibition in the fentanyl group decreased with PCA. Finally, it is unlikely that PCA morphine explains the threshold differences among groups because initial doses were identical and subsequent 24-hour use was similar. This conclusion is supported by the significant differences present five days postoperatively, long after morphine analgesia had ended.

In another study of hysterectomies and isoflurane anesthesia, ketamine- or fentanyl-supplemented patients had similar wound pressure pain thresholds, higher than those for placebo, 24–48 hours postoperatively (10). Meperidine consumption with fentanyl and ketamine, alike throughout, was similar to placebo from three hours postsurgery onward. Spontaneous incisional pain did not differ between groups.

Although wound hyperalgesia reflects both central and peripheral excitation, the results agree with ours in suggesting similar depression of spinal excitation by ketamine and fentanyl. Three further studies of isoflurane anesthesia and hysterectomy have investigated sensory change after surgery (28–30). Two demonstrated spinal excitation (28,30) depressed by morphine preemption (30). One study showed generalized sensory inhibition (29) for a single postoperative measure, in the other (30), absent absolute thresholds preclude conclusions about central sensory inhibition.

The present study confirms the ability of fentanyl to inhibit spinal excitation for abdominal surgery involving both visceral and somatic nociception and suggests that ketamine or magnesium supplementation is also effective for this purpose. For generalized sensory inhibition after surgery, NMDA antagonism may interfere with SIA, and opioid agonism may interfere with DNIC, in agreement with experimental findings (6,8). The effects of all three drugs on the various forms of central sensory inhibition in the surgical context require further investigation. Our results demonstrate the importance of considering inhibition as well as excitation in studying postsurgical changes in sensory processing and their pharmacological modulation. Further studies are required to explore these complex interactions and their relationship to pain and other clinical outcomes after surgery.

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14. *Article* - Preoperative Pain and Preoperative Neuroplasticity

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Preoperative back pain is associated with diverse manifestations of central neuroplasticity

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Abstract

Increased or decreased gain in central nervous system processing after surgery, i.e. neuroplasticity, may play an important role in postoperative pain. Identification of patient subgroups particularly vulnerable to either type of post-surgical neuroplasticity is thus of interest. Preoperative pain has also been suggested to increase vulnerability to post-surgical chronic pain complications due to central facilitation. To study if back pain preoperatively is associated with differences in central sensory processing, we measured transcutaneous electric sensation, pain detection and pain tolerance thresholds at the upper arm, lower back and lower leg in 52 consecutive patients scheduled for back surgery in a blinded, prospective fashion. Patients with no pain had significantly lower pain thresholds than patients with pain in the leg, and significantly higher pain thresholds than those with pain in the back. These results suggest that preoperative pain can induce diverse central neuroplastic changes, i.e. inhibition and facilitation, and that the nature of this neuroplasticity depends on the nature of the pain involved. The presence of facilitation may be the basis of the increased vulnerability described in some studies of patients with significant preoperative pain, whereas the implications of reduced pain sensitivity are less clear. The demonstration of neuroplasticity and its diversity are, however, likely to be of significant clinical relevance. © 2001 Published by Elsevier Science B.V. on behalf of International Association for the Study of Pain.

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1. Introduction

Ongoing nociception can be associated with alterations in peripheral and central nervous system processing (Woolf and Wall, 1986; Raja et al., 1988). In the context of human surgery, such alterations to central nervous system function, termed neuroplasticity, are considered to play a role in postoperative pain (Woolf and Chong, 1993; Wilder-Smith et al., 1996). Neuroplastic changes, particularly facilitation, are also believed to be involved in pain chronification mechanisms, and hence to be of relevance regarding long-term pain outcomes after acute nociception (Coderre et al., 1993). The identification of patient subgroups particularly vulnerable to postoperative neuroplastic change is thus desirable, as such subgroups could benefit from aggressive pre-emptive antinociceptive interventions to improve acute and chronic pain outcomes after surgery.

The presence of chronic pain prior to surgery has been suggested to increase patient vulnerability to chronic pain complications after surgical nociception, although these results remain controversial (Nikolajsen et al., 1997a, 1998; Bach et al., 1988). The increased vulnerability has been postulated to be the result of the pain inducing central neuroplastic change (Nikolajsen et al., 1997b) – without being successfully validated to date, despite various attempts to do so (Nikolajsen et al., 1997a,b, 1998). Therefore, other aspects of neuroplasticity may be involved, such as alterations in the balance between central inhibitory and facilitatory mechanisms (Nikolajsen et al., 1997a,b, 1998). Recent studies outside the surgical context have shown, however, that chronic musculoskeletal pain can be associated with central sensitization and facilitation (Kolbaek Johansen et al., 1999; Graven-Nielsen et al., 2000).

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The presence of central nervous system neuroplastic changes allied to preoperative pain is not proven at present. The aim of this study is to investigate whether preoperative back pain in patients with intervertebral disc prolapse scheduled for surgical treatment is associated with neuroplastic changes manifested as facilitation or inhibition of sensory and nociceptive processing.

2. Methods

In the context of a study of the modulation of the sensory change (neuroplasticity) accompanying back surgery, we prospectively collected 52 consecutive patients scheduled for elective surgery of intervertebral disc prolapse with institutional review board permission and informed patient consent. A detailed history was taken and a thorough physical examination was performed before inclusion in the study. In order to attempt to collect as homogeneous a group of patients as possible, in whom pain – as opposed to neurological deficit – was the predominant problem, we included only patients conforming to the following criteria: (1) significant pain (pain score greater than 5) in the lower back for more than three-quarters of the time for at least 1 month and accompanied by typical sciatic pain radiating into the leg, (2) significant impairment of everyday activities due to this pain for more than three quarters of the time for at least 1 month, (3) local pain/tenderness, muscle stiffness/spasm, and reduced mobility of the lower back on physical examination, (4) positive Lasegue's sign on straight-leg raising on at least one side, and (5) identifiable anatomical intervertebral disc abnormality on neuroimaging. Exclusion criteria included focal neurological motor deficit, peripheral neuropathy and diseases predisposing to peripheral neuropathy such as diabetes mellitus or major alcohol abuse. All patients were started on bed rest and a standard anti-inflammatory scheme of 3 × 100 mg of diclofenac p.o. daily 3 days before surgery and were thus under this regime at the time of inclusion into the study. This course of treatment rendered some patients pain-free some of the time.

The afternoon before surgery, patients were asked about the presence, intensity (verbal pain intensity rating score – VPIRS: 0, no pain; 10, worst imaginable pain) and location (pain predominantly in the back, radiating down the leg, or both) of pain due to the back at that time. The patients were then classified into one of four groups ('pain status') according to the nature of their current pain: no pain ('no pain'; VPIRS < 1), or pain (VPIRS > 1) only in the back ('back pain'), only radiating down the leg ('leg pain') or in both sites ('leg + back pain'). After an explanation and training session, an observer blinded to the patient's pain status then measured their thresholds to transcutaneous constant current electric stimulation (Digistim, Biometer A/S, Copenhagen, Denmark; tetanic stimulation at 100 Hz, 0.2 ms square wave pulses, ramping rate ca. 0.1 mA/s, applied via self-adhesive electrodes 3 cm apart) in an identical fashion and at identical sites in all patients enrolled in the study. Sensation (electric current just felt), pain detection (stimulus just becoming painful) and pain tolerance (stimulus just becoming intolerably painful) thresholds were determined (1) in the middle of a painful leg dermatome (L5-S1), (2) in the lower back, 5 cm from the midline in the T12-L1 dermatome, contralateral and ipsilateral to the side of the nerve root involved, and (3) on the proximal arm (C8-T1 dermatome) contralateral to the nerve root involved. Care was taken not to stimulate major nerves directly. Thresholds were measured consecutively in a run and averaged from three runs separated by 5 min. If two threshold values differed by more than 20% between runs, testing was repeated.

Statistical analysis was performed using the software package Statistica for Windows (release 4.5, Statsoft Inc., 2325 East 13th Street, Tulsa, OK 74104, USA). Patient group data were compared using Student's t-test or the χ^2-test as appropriate, and group thresholds were compared by ANOVA. Post-hoc testing was by Duncan's multiple range test, which incorporates correction for multiple testing. Relationships between thresholds and current VPIRSs in the three pain status groups with pain (i.e. 'leg pain', 'back pain' or 'leg + back pain') were examined via the Spearman R coefficient for non-parametric correlation. For all statistical analysis, significance was assumed for $P < 0.05$. Based on previous results (Wilder-Smith et al., 1996) the present study was predicted to have the ability to identify threshold changes of 20% for a group size of $n = 12$ (alpha = 5%, beta = 20%, two-tailed testing).

3. Results

The patients without pain ('no pain') at the time of inclusion and testing ($n = 27$; age, 41 ± 11 years; height, 172 ± 8 cm; weight, 73 ± 12 kg; sex ratio M/F, 22:5; means ± SD) were similar to all those with pain at that time ('back pain', 'leg pain' or 'leg + back pain') ($n = 25$; age, 46 ± 12 years; height, 172 ± 8 cm; weight, 71 ± 13 kg; sex ratio M/F, 17:8; means ± SD).

ANOVA testing of the thresholds reveals a significant effect for 'pain status' ($P < 0.0000001$). Compared to patients without preoperative pain ('no pain'), thresholds overall are higher in the group with leg pain ($P = 0.00006$), lower in patients with back pain ($P = 0.0001$) and similar in those with mixed pain ('leg + back pain'). As expected, all three types of threshold test (sensation, pain detection or tolerance) are significantly different from each other ($P < 0.0000001$). The site of testing failed to reach a significant effect on thresholds, therefore for simplicity, further results as reported in Fig. 1 combine measures from all test sites. Sensation thresholds do not differ between the four pain status groups, but pain detection and tolerance thresholds are both significantly higher in leg pain patients ('leg pain'), and significantly

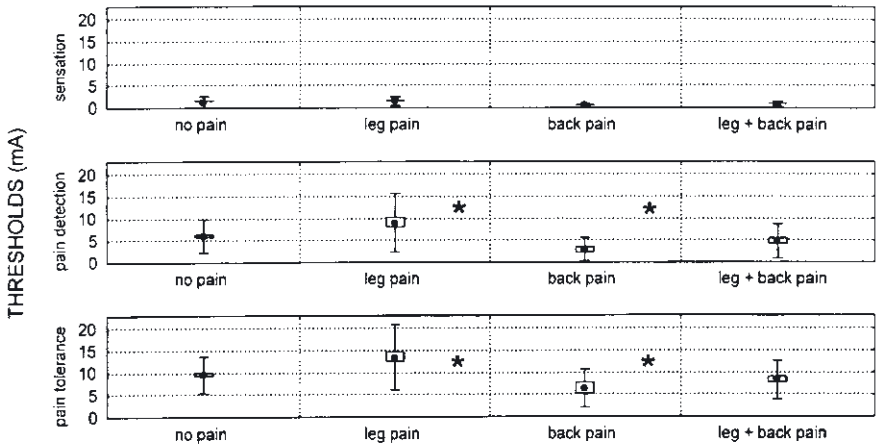

Fig. 1. Boxplots of sensation, pain detection and pain tolerance thresholds (mA; means ± standard errors of the mean ± standard deviations) in the four groups of patients scheduled for back surgery with: no pain ('no pain'), pain only in the leg ('leg pain'), pain only in the back ('back pain'), or pain in both back and leg ('leg + back pain'). *Significantly different from the value in patients without pain (NO, $P < 0.05$).

lower in back pain patients ('back pain') as compared to those without pain ('no pain'; $P < 0.005$ for both comparisons).

The Spearman R correlation coefficients between VPIRSs and thresholds are displayed in Table 1. Because ANOVA testing was unable to demonstrate differences between sites for thresholds, correlations combine thresholds at all sites. Patients with leg pain ('leg pain') show a highly significant negative correlation (Spearman $R > 0.5$, $P < 0.0005$ for fit) between current VPIRSs and pain detection/tolerance thresholds. Current pain scores are not correlated with thresholds in the back pain group ('back pain'), with only a few weak correlations in the group with mixed pain ('leg + back pain').

In no case did threshold measures have to be repeated due to lack of stability in measurement. Comparison of the variability of the threshold measurements in the arm and leg sites revealed similar variances at both sites, taking patients from all pain status groups together (threshold variance: arm, 29.5; leg, 28.1; Levene's test, $P = 0.67$) as well as for only patients with preoperative leg pain (threshold variance: arm, 59.1; leg, 45.7; Levene's test, $P = 0.88$). Based on the pain tolerance threshold data in the patients without preoperative pain, the study has the post-hoc statistical power (alpha = 5%, beta = 20%, two-tailed testing) to detect a threshold difference of 25% with a sample size of $n = 24$.

4. Discussion

This study suggests that preoperative pain in back patients scheduled for prolapsed intervertebral disc surgery is associated with significant changes in central nervous

Table 1
Non-parametric correlations between VPIRS and thresholds to transcutaneous electrical stimulation in the three patient groups with current pain (i.e. 'back pain', 'leg pain', 'leg + back pain') expressed as Spearman R coefficients[a]

Test	Pain	Leg pain		Back pain		Leg + back pain	
		Spearman R	P	Spearman R	P	Spearman R	P
PTT	Leg	− 0.57	0.0001	–	–	− 0.26	0.07
	Back	–	–	0.24	0.5	− 0.26	0.07
PDT	Leg	− 0.53	0.0005	–	–	− 0.32	0.03
	Back	–	–	0.52	0.08	− 0.17	0.24
ST	Leg	− 0.20	0.2	–	–	0.30	0.04
	Back	–	–	0.48	0.1	− 0.38	0.007

[a] P values relate to goodness of fit of correlation. Test, threshold tested (PTT, pain tolerance; PDT, pain detection; ST, sensation); pain, where the pain is located and rated by VPIRS.

system nociceptive processing. Non-nociceptive sensory processing seems to be unaffected. The type of neuroplasticity evoked seems to depend on the nature of the pain, with the more acute pain radiating down the leg allied to an inhibitory response, and the more chronic pain in the back coupled with an excitatory response. This observation of opposite responses with leg or back pain is strengthened by the intermediate position of the pain thresholds in patients with combined back and leg pain. Only in the group with leg pain is there a strong negative correlation between pain thresholds and VPIRSs, in keeping with the increased thresholds in these patients, whereas such a correlation is not present for back pain. Only weak, heterogeneous correlations are seen in the patients with both leg and back pain.

Clearly it is important to take into account the nature of the nociception involved in interpreting the results of quantitative sensory testing in pain research: analysis of the data in the present study without distinguishing the patients by pain type would have revealed no differences between patients without pain and those with (any kind of) pain. It seems logical to assume that the presence of central facilitation before surgery could well render the patients more vulnerable to the subsequent nociception of surgery and its consequences. However, the present study did not include postoperative data, and thus confirmation of such a relationship awaits future studies linking preoperative and postoperative neuroplasticity and their relationship to pain.

4.1. Comparison with other studies

We have been unable to find other studies formally investigating neuroplasticity in patients for prolapsed intervertebral disc surgery. Some literature about low back pain and pain thresholds is available, however. In a recent study, increased sensitivity in pain thresholds was found to explain a large part of the variance not only in pain but also the functional status of chronic low back pain patients (Clauw et al., 1999). Looking at patients with chronic back pain due to lumbosacral disc pathology and hence a high proportion of sciatica (i.e. leg pain), Peters et al. (1992) found significantly elevated pain tolerance thresholds in these patients as compared to normal controls, and Lautenbacher et al. (1990) demonstrated a significant negative correlation between the intensity of current pain and thermal tonic pain thresholds (similar to our electric pain tolerance). These results fit well with ours in associating increased pain sensitivity (facilitation) with more chronic/tonic low back pain, and linking decreased pain sensitivity (inhibition) with the more acute/phasic pain of sciatica.

4.2. Methods and design

Transcutaneous electrical stimulation is a well-established and easy to use technique in human quantitative sensory testing, whose stability, controllability, reliability and simplicity of use makes it well-suited for patients in the clinical context (Lautenbacher and Rollman, 1993; Enggaard et al., 2001). Electrical transcutaneous stimulation might be considered a non-physiological form of sensory stimulation. The stimulation paradigm we chose should stimulate all classes of sensory nerve fibres, particularly, but not exclusively, A-delta and C fibres (Chado, 1995). This may in fact be an advantage in the context of clinical nociception quantification, where an overall, integrated picture of sensory processing is desirable – as opposed, for example, to the selective fibre stimulation of thermal testing. In addition, it has been shown that human thresholds to transcutaneous electrical stimulation are sensitive to central excitatory as well as inhibitory phenomena, both clinically and experimentally (de Broucker et al., 1990; Wilder-Smith et al., 1996). In contrast, various studies have shown and remarked upon the relative insensitivity of, for example, thermal stimulation to inhibitory phenomena (Lascelles et al., 1997; Kosek and Ordeberg, 2000; Wilder-Smith, 2000).

Every effort was made in this study to ensure the validity and reproducibility of the threshold measures, including careful patient instruction and training, measures being performed by only two persons, the average of three measurement runs being used, and choosing a slow ramping rate for electrical stimulation to reduce overshoot as much as possible. Our testing paradigm was designed to avoid inducing sensitization by stopping stimulation on reaching the pain tolerance threshold and not using suprathreshold stimulation. If the results of two runs in the series of three differed by more than 20%, the measures were repeated – and this was never necessary, suggesting good short-term threshold stability in this study. The variability of our measures is in accordance with the literature (Lautenbacher and Rollman, 1993; Enggaard et al., 2001).

It might have been anticipated that thresholds in the leg site would differ from the other sites due to sciatica. While the absolute numbers for the thresholds in the leg are different from the other sites, these differences do not achieve statistical significance, most likely because the size of the difference falls below the detection power of the study (e.g. due to subject numbers and necessity of correcting for multiple statistical testing). Interestingly, threshold variances were the same at all measurement sites including the leg, in contrast to the higher variability that might have been expected in the leg in the presence of neuropathic pain (Greenspan, 2001). It should also be noted that, due to their pain history, the group without pain just preoperatively is unlikely to have the same thresholds as normal healthy subjects – but this remains to be confirmed in future studies.

4.3. Central neuroplasticity: facilitation

In animal models, central sensitization can be produced by nociceptive input from musculoskeletal structures (Hoheisel and Mense, 1990; Neugebauer and Schaible, 1990). We now have increasing evidence from patient

studies that chronic nociceptive input from musculoskeletal structures (including, for example, in low back pain) is also associated with facilitation of central nervous system sensory processing (Brands and Schmidt, 1987; Lautenbacher et al., 1990; Maixner et al., 1995; Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997; Graven-Nielsen et al., 2000; Kosek and Ordeberg, 2000). Sensitization in such patients is demonstrable via reduced thresholds as compared to normal controls in both superficial (Kosek and Ordeberg, 2000) and deep (Kolbaek Johansen et al., 1999; Graven-Nielsen et al., 2000) structures. The results are further supported by the beneficial, sensitization-reducing effects of NMDA receptor blockade in chronic whiplash syndrome patients (Graven-Nielsen et al., 2000), and the reversal of central sensitization 9 months after pain-relieving surgery in patients with chronic osteoarthritis (Kosek and Ordeberg, 2000). These findings are in good agreement with the facilitated central nervous system nociceptive processing found in our patients with pure low back pain.

4.4. Central neuroplasticity: inhibition

Acute nociceptive input in animals – including that from musculoskeletal structures – can also activate central descending inhibitory systems (Hoheisel and Mense, 1990; Neugebauer and Schaible, 1990; Schaible et al., 1991). The best-described example is 'diffuse noxious inhibitory controls' (DNIC), in which spinal dorsal horn wide dynamic range (WDR) neurones undergo strong inhibition originating from supraspinal structures after acute heterotopic noxious conditioning stimuli (Le Bars et al., 1979a,b). Studies are now available suggesting that chronic radicular pain retains the ability to elicit such an inhibitory response, perhaps due to its intense but intermittent nature (Voerman et al., 2000). For chronic pain involving less intense but more continuous nociceptive input, the facilitation due to ongoing nociceptive activity may be augmented by impaired descending central pain inhibition (Maixner et al., 1995; Kosek et al., 1996), with a return to normal once chronic nociceptive input ceases (Kosek and Ordeberg, 2000). Results supporting this concept have been published for chronic low back (Brands and Schmidt, 1987) and other chronic musculoskeletal pain syndromes (Maixner et al., 1995; Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997; Kosek and Ordeberg, 2000). Our results in patients with mixed leg and back pain are compatible with an impaired ability of acute nociception (e.g. leg pain) to elicit inhibitory responses in the presence of chronic nociception (e.g. low back pain).

4.5. Correlations between thresholds and clinical pain measures

Weak relationships between subjective clinical pain measures (e.g. pain scores or scales) and psychophysical measures (e.g. thresholds) have frequently been observed in the relevant literature (e.g. Wilder-Smith et al., 1996; Yarnitsky et al., 1996; Nikolajsen et al., 1998), which findings correspond well with our results in patients with pure or mixed back pain. In view of the accepted multifactorial nature of the subjective pain experience this is hardly surprising. Of interest is the much closer inverse relationship between current subjective pain rating and pain thresholds in the patients with pure leg pain in our study. Such a link, not previously described in this form, may be the result of the leg pain acting as a heterotopic nociceptive conditioning stimulus eliciting an acute inhibitory central response, thus better maintaining stimulus–response relationships. The much weaker relationship in the patients with mixed pain might then possibly be due to impairment of central inhibitory mechanisms as discussed above.

In summary, we have been able to demonstrate evidence for central neuroplasticity in patients with back pain before surgery. The type of neuroplasticity present differs according to the predominant site and type of pain reported by the patient, with the more chronic/tonic back pain being associated with central sensitization, and the more acute/phasic pain radiating down the leg being allied with a central inhibitory response. The implications of this discovery for postoperative neuroplasticity and pain and its longer-term outcome consequences need to be investigated.

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15. *ARTICLE* – PAIN, ANALGESIA AND POSTOPERATIVE NEUROPLASTICITY

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QUANTITATIVE SENSORY TESTING AFTER HUMAN SURGERY: EFFECTS OF PREOPERATIVE PAIN AND ANALGESIC MANAGEMENT

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ABSTRACT

Alterations in central sensory processing after nociception are complex and potentially a significant factor in postoperative pain. We investigated the course of these alterations after human surgery and how preoperative pain or analgesia affect them using quantitative sensory testing, and compared them with clinical pain measures.
Patients with “minor” (VAS<3) or “major” (VAS≥3) pain before back surgery received placebo, fentanyl or ketorolac (n=15/group) before isoflurane-nitrous oxide anaesthesia.

Preoperatively to 5 days postoperatively, we measured absolute and relative (normalisation to arm) thresholds to electrical skin stimulation at incision site, arm and leg, and pain scores and morphine PCA consumption (24 hours postoperatively).
Absolute thresholds increased maximally 4 hours, and decreased maximally 5 days after surgery (+42%; -49%; $P<0.00005$ vs. preoperatively). Increases were largest with fentanyl ($P<0.003$), and differences between maximum and minimum values greatest with major preoperative pain ($P=0.03$). Placebo patients with minor preoperative pain showed threshold decreases postoperatively (relative: 1h - 5d; absolute: 24h - 5d); major preoperative pain and fentanyl inhibited these. With ketorolac, absolute thresholds decreased (24h - 5d) despite prevention of relative threshold reductions. Patients with major preoperative pain had less early leg pain, and used more morphine in total with ketorolac than fentanyl (+134%, $P<0.05$).
Patients with minor preoperative pain exhibit spinal and supraspinal excitation after surgery under non-analgesic anaesthesia. Major preoperative pain and fentanyl inhibits such changes. Ketorolac depresses spinal facilitation, but not late generalised hyperalgesia. Postoperative sensory change is only partially expressed in clinical pain measures, suggesting the usefulness of including quantitative sensory testing in future research.

Key Words
Pain: preoperative, postoperative, clinical, measurement
Quantitative sensory testing: transcutaneous electrical thresholds
Surgery: human, nociception, analgesia
Analgesics: fentanyl, ketorolac

1. INTRODUCTION

Acute and chronic nociception alter peripheral and central nervous system function (Raja et al., 1988; Coderre et al., 1993). Animal studies have shown post-nociceptive changes in central nervous system processing to be complex, varying according to time after nociception, showing both inhibitory and excitatory patterns, and affecting spinal as well as supraspinal structures (Coderre et al., 1993; Richmond et al., 1993; Jayaram et al., 1995; Woolf and Salter, 2000). Altered central sensory processing due to nociception is considered to play an important role in the aetiology of pain after surgery in humans, and has been postulated to be a potentially significant factor in determining acute - and perhaps chronic - postoperative pain outcomes (Coderre et al., 1993; Woolf and Chong, 1993; Woolf and Salter, 2000).

Extrapolation from animal data in this context is fraught with difficulty, as demonstrated by the pre-emptive analgesia debate, making the collection of actual human data necessary (Wall, 1988; Kehlet, 1994; McQuay 1995; Urban and Gebhart, 1999; Wilder-Smith, 2000). However, human data as to the course and nature of altered central sensory processing after surgery remain sparse. Furthermore, the relationship between objective measures of altered central processing (e.g. psychophysical, electrophysiological meas-

ures) and the inevitably subjective measures of pain experience (e.g. pain scores, analgesia use) after surgery is poorly understood. Finally, the effects of clinically typical and relevant factors such as preoperative pain and/or analgesic management on postoperative central sensory processing are largely uninvestigated.

Thus the first aim of the present clinical study, which bases upon and expands earlier research (Wilder-Smith et al., 1996), is to investigate the time course of changes in supraspinal and spinal central nervous system sensory processing up to 5 days after surgery, as measured by quantitative sensory testing (QST) using thresholds to cutaneous electric stimulation. A second goal is to study the effects on these postoperative processing alterations of two common, clinically relevant factors, acute preoperative pain and preoperative analgesia (i.e. fentanyl, an opioid, and ketorolac, an NSAID). A final purpose of the study is to permit comparison between postoperative QST alterations and postoperative pain, as measured by clinical pain measures such as scores and analgesia consumption.

2. MATERIALS AND METHODS

2.1. Study design and patients

Using a prospective, randomised, placebo-controlled and double-blinded design and after institutional review board approval we studied 45 ASA 1 and 2 patients scheduled to undergo elective surgery for intervertebral disc herniation. The surgical procedure (fenestration, removal of disc fragments) was standardised and the same for all patients. Patients were recruited the afternoon before surgery and gave written informed consent. A detailed history and physical examination was performed. To recruit a homogeneous group in whom pain - as opposed to neurological deficit - was the main symptom over time, patients conformed to the following criteria: 1) significant pain over the last month (score greater than 5, in the lower back, for more than three quarters of the time for at least one month, accompanied by typical sciatic pain radiating into the leg), 2) significant impairment of everyday activities due to this pain (for more than three quarters of the time, for at least one month), and 3) significant and typical findings on physical examination (local lower back pain/tenderness, muscle stiffness/spasm, reduced mobility; positive Lasegue's sign on at least one side). An additional indication for surgery was identifiable anatomical intervertebral disc abnormality on neuroimaging. Exclusion criteria included significant focal neurological motor deficit, peripheral neuropathy and diseases predisposing to peripheral neuropathy such as diabetes mellitus or major alcohol abuse. Bed rest and a standard anti-inflammatory scheme of 3x100mg of diclofenac p.o. daily were started in all patients 3 days before surgery. Patients were thus under this regime at the time of inclusion into the study, with some patients being rendered pain-free some of the time by this course of treatment.

2.2. Patient groups

Patients received no premedication on the morning of surgery. On entering the operating theatre, they were randomised into three drug groups by computer-generated randomi-

sation table (n = 15 per group). Patients received a blinded short infusion of either 100 ml 0.9% NaCl (placebo group), 3 $\mu g.kg^{-1}$ fentanyl in 100 ml 0.9% NaCl (fentanyl group), or 30 mg ketorolac in 100 ml 0.9% NaCl (ketorolac group). This infusion was prepared by a nurse otherwise not involved in the study to assure blinding.

Before insertion of intravenous access, patients were asked about the presence and intensity of pain due to the back (verbal pain intensity rating score: 0 = no pain; 10 = worst imaginable pain). Based on this answer, patients were classified as having "minor" (VAS<3) or "major" (VAS≥3) preoperative pain (preoperative pain status).

2.3. Threshold determination

Next, taking care not to stimulate major nerves directly, an observer blinded to the patient's pain status determined thresholds to transcutaneous constant current electric stimulation (Digistim, Biometer A/S, Copenhagen, Denmark; tetanic stimulation at 100Hz, 0.2 ms square wave pulses, ramping rate ca. 0.1mA/s, applied via self-adhesive electrodes 3 cm apart). Thresholds were determined for sensation, pain detection and pain tolerance (electric current just felt; just becoming painful; and just becoming intolerably painful; respectively). They were measured at leg, (proposed) surgical incision and arm sites (L5-S1 dermatome: point of maximum leg pain; T12-L1 dermatome: 5 cm from midline incision, contralateral and ipsilateral to the side of the nerve root involved; and C8-T1 dermatome, contralateral to the nerve root involved; respectively). Thresholds were quantified consecutively in a run in an identical fashion and at identical sites in all patients. The average of three runs separated by five minutes was used for analysis. If two threshold values differed by more than 20% between runs, testing was repeated until stable.

Absolute, unmodified threshold values were used to evaluate generalised changes in central sensory processing due to supraspinal but also spinal effects. To assess segmental, spinal threshold changes we (mathematically) removed generalised effects by normalisation to a site distant from surgery (i.e. the arm site). Thus relative thresholds were calculated by dividing the threshold value at the site in question by the corresponding value at the arm.

2.4. Anaesthesia and analgesia

Venous access was established and the patient received the blinded short infusion. Approximately ten minutes later, anaesthesia was induced with thiopental 5 $mg.kg^{-1}$ followed by vecuronium 0.1 $mg.kg^{-1}$. After tracheal intubation, isoflurane and nitrous oxide in oxygen were used to maintain anaesthesia as necessary. No other drugs were used for anaesthesia which always lasted less than one hour in total. Morphine patient-controlled analgesia (PCA) was started in the post-anaesthesia care unit and continued until 24 hours postoperatively (loading bolus: 60 $\mu g.kg^{-1}$, demand bolus: 25 $\mu g.kg^{-1}$, lock-out time: 8 minutes). For the period of morphine PCA, patients did not receive any other analgesics.

During the first two hours' stay in the post-anaesthesia care unit, a background infusion of morphine 15 $\mu g.kg^{-1}.h^{-1}$ was used. This was discontinued on transfer to the ward, and the lock-out interval increased to 15 minutes. After 24 hours, analgesia was continued to day 5 by oral diclofenac at 3X100 mg p.o. only.

2.5. Times of measures

At 1, 2, 4, 6, and 24 hours and 5 days after extubation, thresholds, pain verbal intensity rating scores in leg and back, observer sedation rating scores (5 = wide awake, 1 = unrousable), and cumulative morphine consumption (except day 5) were measured as described above.

2.6. Statistical analysis

Based on previous results (5) the present study was predicted to have the ability to identify threshold changes of 20% for a group size of n=12 (alpha=5%; beta=20%; two-tailed testing). Statistical analysis was performed using the software package Statistica for Windows (release 4.5, Statsoft Inc., 2325 East 13th Street, Tulsa OK 74104, USA). Patient group demographic data were compared using ANOVA or Kruskal-Wallis ANOVA-testing as appropriate. Baseline absolute and relative thresholds were compared using 4-way ANOVA (factors: drug group, measurement site, threshold type, preoperative pain status) with post hoc Tukey Honest Significant Difference testing. Changes in group absolute and relative thresholds were analysed using repeated measures 5-way ANCOVA (co-variant: preoperative control thresholds; factors: drug group, measurement site, threshold type, preoperative pain status, time) and post hoc Tukey testing. Pain and drug group differences in morphine consumption were tested for using 3-way repeated measures ANOVA (factors: drug group, preoperative pain status, time) with post hoc Tukey testing. Pain verbal intensity rating scores and observer sedation scores were compared between groups using Kruskal-Wallis ANOVA, with Bonferroni-corrected post hoc Mann-Whitney U testing as necessary. For all statistical analysis, significance was assumed for $P<0.05$, correlations for $R>0.6$ were considered significant.

3. RESULTS

3.1. Patient characteristics

Patient demographics were similar in the three drug groups (placebo: age = 48±13 years, weight = 74±13 kg, height = 172±10 cm, male:female = 9:4, no pain:pain = 10:3; fentanyl: age = 41±11 years, weight = 74±15 kg, height = 174±8 cm, male:female = 12:3, no pain:pain = 11:4; ketorolac: age = 45±12 years, weight = 72±11 kg, height = 170±6 cm, male:female = 10:3, no pain:pain = 10:3). Two placebo and two ketorolac group patients had incomplete pain data and were excluded from analysis.

3.2. Generalised sensory change: absolute threshold values

3.2.1. Baseline values

Baseline preoperative absolute threshold values did not differ according to drug group, site of threshold testing or preoperative pain status. As covariant, preoperative thresh-

Table 1: Factors significantly affecting thresholds

a. absolute thresholds

factor(s)	*significance*
drug group	*P*=0.0005
test type	*P*<0.000001
preoperative pain status	*P*=0.03
time	*P*<0.000001
drug group x preoperative pain status	*P*=0.001
drug group x time	***P<0.000001***
test type x time	*P*<0.000001
drug group x preoperative pain status x time	*P*=0.00006

b. relative thresholds

factor(s)	*significance*
test type	***P=0.00002***
time	***P=0.02***
test type x time	*P*=0.0003
preoperative pain status x time	***P=0.01***
drug group x test type x time	***P=0.006***
drug group x preoperative pain status x time	***P=0.0008***

Single and combined factors with significant effects on absolute and relative (i.e. normalised by division by arm threshold values) postoperative thresholds (ANCOVA).

olds were significantly and inversely related to threshold changes 24 hours and 5 days after surgery (pooled within-groups correlations of -0.73 and -0.82, respectively). As to be expected, baseline thresholds differed according to the type of threshold tested.

3.2.2. Overall factor effects

Overall postoperative change in absolute thresholds was highly significantly affected by the single factors drug group, type of threshold tested, preoperative pain status, and time (Table 1). Post hoc testing revealed thresholds to be most increased in the fentanyl group

(+41% vs. preoperative baseline; placebo: +29%; ketorolac +28%; $P<0.003$ vs. fentanyl), and the difference between maximum and minimum values to be greatest with minor preoperative pain ($P=0.03$ for minor vs. major preoperative pain). Absolute thresholds reached their maximum 4 hours (+42%) and their minimum 5 days postoperatively (-49%) ($P<0.00005$ for both vs. preoperative baseline). Site of threshold measure failed to have a significant effect on postoperative absolute threshold change, either singly or in combination with other factors, thus it is not further considered in analysis. Increases and decreases of absolute thresholds were most marked and significant for pain tolerance, less so for pain detection, and not significant for sensation, thus only results for pain tolerance thresholds are displayed for the graphs of generalised sensory change.

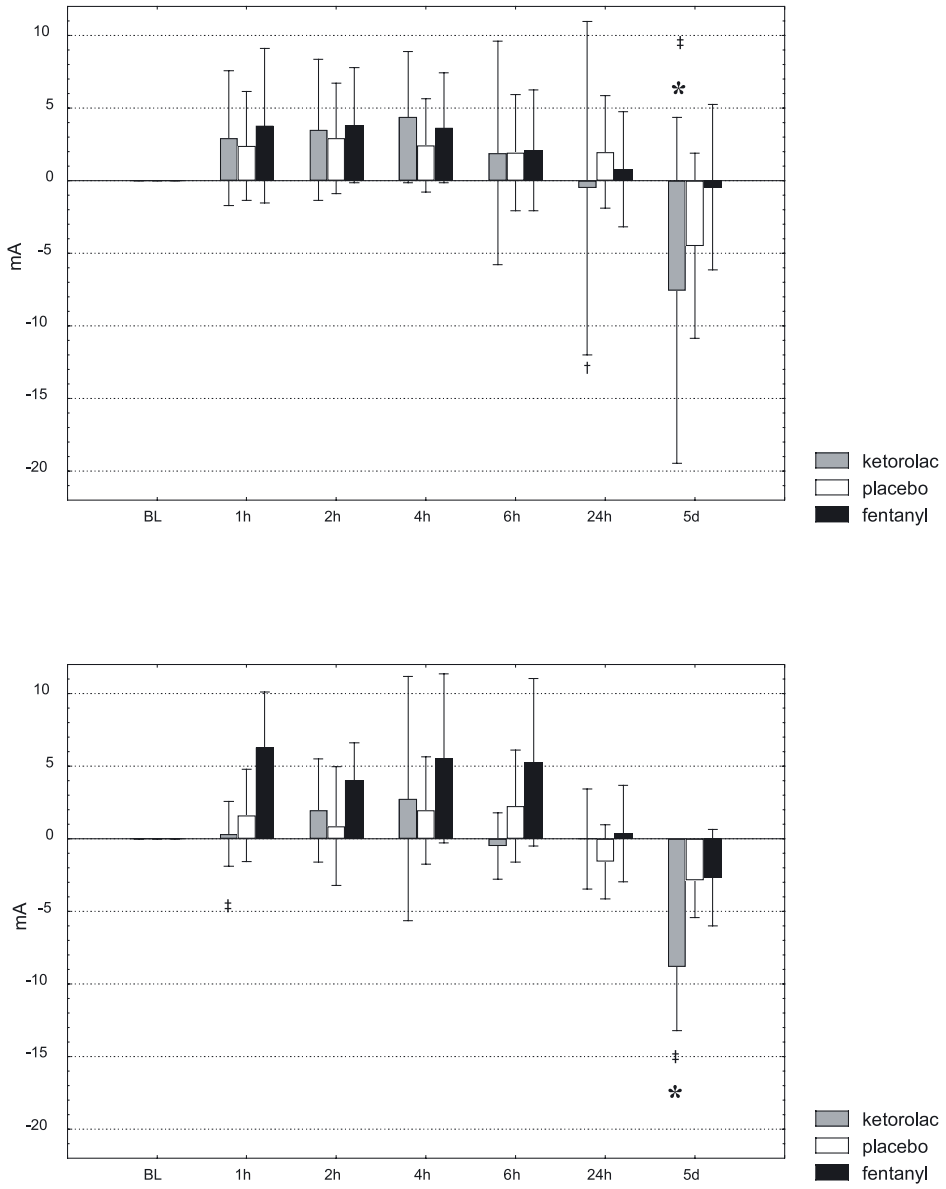
3.2.3. Changes with minor preoperative pain

In the placebo group, absolute thresholds taken together neither increased nor decreased significantly during the first 24 hours postoperatively. They were significantly decreased compared to preoperatively at 5 days after surgery. With preoperative fentanyl analgesia there were no significant threshold changes at any time postoperatively. Overall thresholds in the ketorolac group were significantly raised 1-4 hours postoperatively, and decreased at 5 days post-surgery. Furthermore, thresholds in the ketorolac group were lower than in the other two groups 24 hours to 5 days postoperatively. The postoperative changes in absolute pain tolerance thresholds with minor preoperative pain are detailed in the top half of Figure 1.

3.2.4. Changes with major preoperative pain

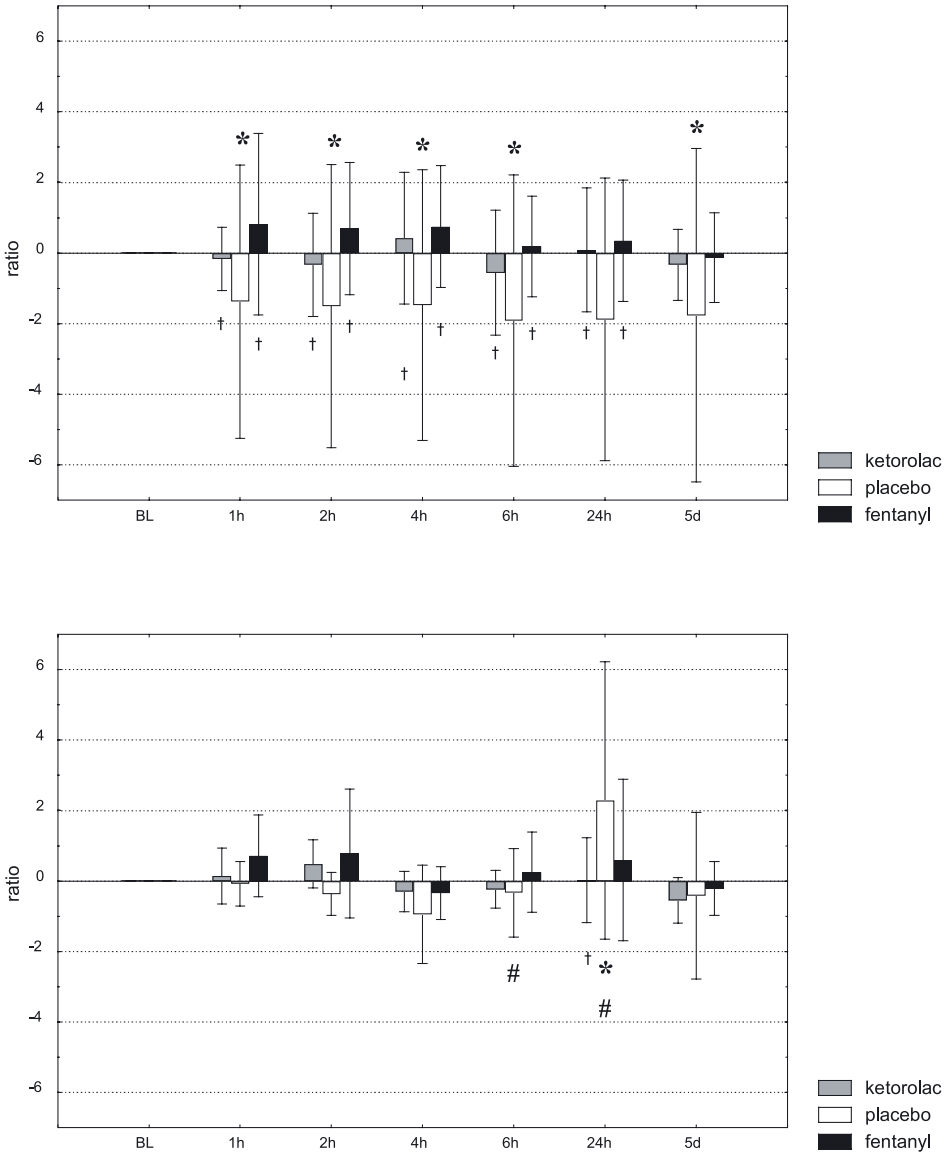
Placebo group absolute thresholds were not significantly altered at any time postoperatively. Fentanyl supplementation was associated with significant increases at 1 and 4 hours postoperatively, without subsequent decreases. In patients receiving ketorolac preoperatively, absolute thresholds taken together were unchanged 1-24 hours postoperatively; being decreased at 5 days compared to preoperatively as well as to the fentanyl and placebo drug groups. The postoperative changes in absolute pain tolerance thresholds with major preoperative pain are detailed in the bottom half of Figure 1.

Figure 1: Absolute thresholds with minor or major preoperative pain



Change in absolute pain thresholds postoperatively (means, SD) in patients with minor (top) or major (bottom) preoperative pain receiving either placebo, fentanyl or ketorolac preoperatively. * = P<0.05 vs. control, † = P<0.05 vs. placebo group, ‡ = P<0.05 vs. fentanyl group.

Figure 2: Relative thresholds with minor or major preoperative pain



Change in relative pain thresholds postoperatively (means, SD) in patients with minor (top) or major (bottom) preoperative pain receiving either placebo, fentanyl or ketorolac preoperatively. * = P<0.05 vs. control, # = P<0.05 vs. patients without pain, † = P<0.05 vs. placebo group.

3.3. Segmental sensory change: relative threshold values

3.3.1. Baseline values

Baseline values for relative thresholds did not differ according to drug group, site of threshold testing or preoperative pain status. As covariant, preoperative thresholds were significantly and inversely related to threshold changes during the entire postoperative period (pooled within-groups correlations: 1h = -0.68, 2h = -0.77, 4h = -0.79, 6h = -0.83, 24h = -0.73, 5 days: -0.89). As expected, thresholds differed significantly according to the type determined.

3.3.2. Overall factor effects

Postoperative changes in relative thresholds were significantly affected by the single factors test type and time (Table 1). Relative threshold changes were most marked for (non-nociceptive) sensation, not being significant for pain detection or tolerance, thus only results for sensation thresholds are displayed for the graphs of spinal neuroplasticity. As site of threshold measure had no significant effect on postoperative relative threshold change, either singly or in combination with other factors, it is not further considered in analysis.

3.3.3. Changes with minor preoperative pain

Relative thresholds overall were lower in the placebo group than in the other two drug groups 4 and 24 hours postoperatively. Relative sensation thresholds in placebo patients were significantly decreased compared to both preoperative baseline and the other two groups 1 hour to 5 days postoperatively (Figure 2, top half). The lowest value was reached 24 hours postoperatively (-56%, P=0.00006 vs. preoperatively; fentanyl: +19%, ketorolac: +6%, P=0.00006 both vs. placebo). Relative pain detection and tolerance thresholds in all 3 groups remained unchanged throughout.

3.3.4. Changes with major preoperative pain

For placebo group patients, relative thresholds overall at 24 hours postoperatively were significantly increased compared to both preoperative baseline and the ketorolac group. There were no significant overall relative threshold changes compared to preoperative baseline in the other two drug groups. The postoperative changes in relative sensation thresholds with major preoperative pain are detailed in the bottom half of Figure 2.

3.4. Clinical pain measures

Cumulative PCA morphine consumption (Table 2) was significantly affected by the interaction of the factors drug group, preoperative pain status and time (P=0.02). Patients with major preoperative pain receiving ketorolac used over twice as much morphine in 24 hours than those receiving fentanyl (P=0.003). Preoperative baseline pain scores in leg and back were similar in the three drug groups (Table 3). Postoperative back pain scores were similar between drug groups throughout. This was true both overall and analysing patients with and without preoperative pain separately. However, for leg pain, patients with major preoperative pain had significantly lower scores than those with minor pre-

operative pain at 1, 4, and 6 hours postoperatively, without differences due to drug group. Sedation scores did not differ at any time according to drug or pain group, and median scores had returned to preoperative baseline values by 4 hours postoperatively.

4. DISCUSSION

This study shows that surgery in humans is followed by complex changes in central nervous system sensory processing. The results of this study suggest the feasibility of using quantitative sensory testing at multiple sites in the clinical surgical context to follow the course of both generalised and segmental changes in central sensory processing, with the former likely reflecting mainly supraspinal but also spinal effects, and the latter, spinal effects. As far as we are aware, our study is the first to investigate the diverse effects of preoperative pain and preoperative analgesia on supraspinal and spinal changes in central sensory processing at different phases of the postoperative process.

For patients with only minor pain preoperatively, surgery performed under volatile general anaesthesia without analgesic supplementation and 24 hours of postoperative morphine PCA analgesia is followed by segmental excitation lasting for the 5 days of the study, with generalised spread of excitation (significant generalised hyperalgesia) becoming apparent after 24 hours. The size of both the generalised and segmental threshold changes is significantly and negatively correlated with preoperative threshold levels. The presence of major pain preoperatively inhibits segmental (spinal) excitation, with suppression of subsequent generalised hyperalgesia, too. Preoperative analgesic supplementation with fentanyl suppresses both generalised and segmental facilitation, also increasing acute early postoperative generalised inhibition in synergy with major preoperative pain. The effects of ketorolac are more complex. Despite suppressing segmental excitation, ketorolac is paradoxically associated with more generalised excitation at 5 days. In addition, there is evidence of an antagonistic interaction between the acute early postoperative generalised inhibition it causes and the presence of major preoperative pain.

Patients with major pain before surgery had less pain in the leg during the early hours following surgery. More PCA morphine was used from 6 hours postoperatively onwards with ketorolac as compared to fentanyl supplementation in patients with major preoperative pain. The time course of postoperative clinical pain measures therefore only partially and incompletely reflects the postoperative time course of alterations in central sensory processing as demonstrated by threshold measures. Thus measures of altered sensory processing (e.g. thresholds, quantitative sensory testing) provide new insight into postoperative pain mechanisms, and will likely need to be a necessary complement to clinical pain measures (e.g. pain scores, analgesia use) in future investigation and management of perioperative nociception.

4.1. Postoperative sensory change with minor preoperative pain and without analgesia

With minor preoperative pain and in the absence of preoperative analgesic supplementation of anaesthesia, we have demonstrated underlying segmental excitation up to 5 days postoperatively, accompanied by significant generalised hyperalgesia after the first 24 hours. As investigation of these aspects of postoperative sensory change is still in its very early stages, our discussion of the possible mechanisms involved will of necessity be speculative. At least some of the continuing facilitation is likely to be the result of ongoing wound nociception in the postoperative period. The waning of supraspinal inhibition with increasing time after the start of nociception could also contribute (Danziger et al., 2001). Another factor might be that morphine analgesia during the first 24 hours, while being unable to completely suppress the establishment of segmental excitation due to ongoing nociception, does prevent the rostral spread of nociceptive excitation. This possibility is supported by the fact that segmental excitation was mainly apparent in non-nociceptive processing (i.e. sensation thresholds), as expected in view of the selective depression of nociceptive processing by opioids, particularly at the spinal level (van der Burght et al., 1994). After the end of morphine analgesia, supraspinal spread of facilitation could then take place in this hypothesis, leading to generalised hyperalgesia. A possible argument against such a scenario would be the continuing presence of non-nociceptive - but not nociceptive - segmental facilitation at 5 days postoperatively. However, it could be that subsequent diclofenac analgesia, while being unable to block rostral facilitatory spread, is able to depress (mainly nociceptive) segmental spinal facilitation up to day 5. Such an interpretation would be in accordance with findings in the present study concerning ketorolac (also an NSAID), which proved unable to block generalised facilitation despite inhibiting segmental facilitation (nociceptive more than non-nociceptive). It should be emphasised that these considerations are at present speculative and that conclusive elucidation of mechanisms involved awaits further studies.

4.2. Major preoperative pain and postoperative sensory change

Acute major preoperative pain in the absence of preoperative analgesic supplementation of anaesthesia resulted in significant depression of postoperative segmental excitation and absence of generalised hyperalgesia after 24 hours. In animal models, acute pain has been demonstrated to elicit strong supraspinal inhibitory mechanisms which can effectively inhibit spinal facilitation (Gall et al., 1999; Gozariu et al., 2000; Danziger et al., 2001). Major preoperative pain may have sufficiently stimulated or activated inhibitory mechanisms to depress spinal excitation due to intra- and early postoperative nociception, thus ultimately preventing subsequent generalised hyperalgesia. The supraspinal inhibitory mechanisms involved are likely to be distinct from diffuse noxious inhibitory controls (DNIC, which originate in the caudal medulla (Bouhassira et al., 1995)) because in our study they are increased with preoperative fentanyl (opioids reduce DNIC (Le Bars et al., 1992)).

Table 2: Postoperative morphine PCA consumption

time postop	*control*	*1h*	*2h*	*4h*	*6h*	*24h*
Cumulative morphine PCA use (mg)						
MINOR PREOPERATIVE PAIN						
ketorolac	0 (0)	7.2 (2.6)	11.1 (6.5)	16.3 (8.3)	20.0 (8.1)	32.7 (15.1)
placebo	0 (0)	6.0 (2.0)	9.4 (3.3)	15.3 (5.3)	18.8 (6.5)	35.3 (12.6)
entanyl	0 (0)	6.0 (1.2)	9.4 (4.1)	15.1 (6.4)	19.5 (9.3)	42.0 (32.1)
MAJOR PREOPERATIVE PAIN						
ketorolac	0 (0)	5.5 (2.3)	11.0 (4.9)	16.9 (3.7)	21.8 (3.4)	59.1‡ (19.3)
placebo	0 (0)	6.3 (3.9)	10.2 (7.8)	13.8 (10.5)	16.9 (12.1)	32.7 (19.2)
fentanyl	0 (0)	7.6 (2.5)	12.4 (7.7)	21.6 (14.6)	23.3 (19.8)	25.3 (14.0)

Time course of postoperative cumulative morphine use (mg) by patient-controlled analgesia (PCA). Values are means (standard deviations). ‡ = P<0.05 vs. fentanyl group.

4.3. Preoperative fentanyl and postoperative sensory change

Fentanyl supplementation preoperatively suppressed postoperative segmental excitation and subsequent generalised hyperalgesia. In the presence of major preoperative pain it also increased generalised hypoalgesia in the early postoperative hours. These effects are in keeping with the well-documented spinal and supraspinal inhibitory actions of opioids, which include positive interactions with various types of supraspinal stress- and nociception-induced analgesia other than classic DNIC (Coderre et al., 1993; Grisel et al., 1993; Woolfolk and Holtzman, 1993; Jayaram et al., 1995; Gozariu et al., 2000).

4.4. Preoperative ketorolac and postoperative sensory change

Postoperative segmental excitation was suppressed in patients receiving ketorolac. Paradoxically, from 24 hours onwards significant generalised hyperalgesia was present, greater than for placebo (or fentanyl) patients. In the presence of major preoperative pain, early postoperative acute generalised inhibition was decreased, with less segmental inhibition than in placebo patients at 24 hours. While NSAIDs have been shown to be able to suppress spinal sensitisation (Malmberg and Yaksh, 1992; Bustamente et al., 1996), they may not be able to prevent supraspinal spread of facilitation with overt generalised hyperalgesia after the ending of morphine analgesia. This possibility is supported by reports that prostaglandin synthesis inhibiting drugs such as NSAIDs can antagonise supraspinal stress- or nociception-induced analgesia (Bhattacharya et al, 1978; Bustamente et al., 1997).

Table 3: *Postoperative verbal pain intensity scores in leg and back*

time postop	*control*	*1h*	*2h*	*4h*	*6h*	*24h*	*5d*
LEG - Verbal pain intensity rating score (min = 0; max = 10)							
MINOR PREOPERATIVE PAIN							
ketorolac	0 (0-2)	2 (0-4)	1.5 (0-5)	0.5 (0-6)	0.5 (0-4)	0 (0-6)	0 (0-3)
placebo	0 (0-2)	2 (0-6)	2 (0-6)	2 (0-6)	0.5 (0-3)	1 (0-4)	1 (0-4)
fentanyl	0 (0-3)	2 (0-6)	0 (0-5)	0 (0-4)	0 (0-5)	1 (0-3	3 (2-5)
MAJOR PREOPERATIVE PAIN							
ketorolac	4 (0-5)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)
placebo	6 (5-7)	0 (0-1)	2 (0-4)	0 (0-1)	0 (0-1)	1 (0-1)	1 (0-7)
fentanyl	7.5 (2-10)	1 (1-1)	0.5 (0-2)	0 (0-0)	0 (0-0)	0 (0-8)	0 (0-0)
BACK - Verbal pain intensity rating score (min = 0; max = 10)							
MINOR PREOPERATIVE PAIN							
ketorolac	0 (0-1)	3.5 (0-7)	2.5 (0-3)	2 (0-6)	1 (0-4)	1 (0-6)	0 (0-3)
placebo	0 (0-2)	5 (2-7)	3 (1-6)	2 (0-6)	2 (0-3)	2.5 (0-5)	1 (0-2)
fentanyl	0 (0-2)	4 (0-10)	3 (0-8)	3 (0-6)	3 (0-8)	1 (0-6)	1.5 (0-4)
MAJOR PREOPERATIVE PAIN							
ketorolac	2 (0-5)	6 (5-7)	5 (3-8)	2 (1-5)	2 (2-4)	1 (0-3)	1 (1-1)
placebo	0 (0-7)	4 (3-8)	3 (2-5)	4 (2-5)	4 (3-6)	3 (2-5)	1 (1-1)
fentanyl	0 (0-5)	5 (1-8)	3.5 (0-7)	5 (0-5)	2.5 (0-7)	2.5 (0-10)	0 (0-2)

Time course of verbal pain intensity rating scores in leg and back. Scores are medians (ranges).

4.5. Comparison with other studies

To the best of our knowledge, this is the first study to formally investigate the effects of preoperative pain on postoperative changes in central sensory processing in the clinical surgical context. Few other human studies of sensory change after surgery are available at present. Early human studies demonstrate isolated segmental hyperalgesia to mechanical or electrical stimulation (Dahl et al., 1993; Richmond et al., 1993) or generalised inhibition using electrical stimulation (Willer et al., 1985; Lund et al., 1990; Peters et al., 1992) once or twice postoperatively. Subsequent more detailed studies document the presence of segmental excitation, abolished by opioid agonist or NMDA antagonist supplementation, which also increases generalised hypoalgesia within the first 24 hours postoperatively (Wilder-Smith et al., 1996; Wilder-Smith et al., 1998).

4.6. Study design

The results of the study might have been influenced by the sensory testing paradigm, considerations of statistical power, and postoperative drug effects. We chose electrical stimulation because it is stable and reproducible, is easy to use and control clinically, has a long history of utilisation and validation, and may be more sensitive to descending inhibition than other modi (Maresca and Faccani, 1983; Lautenbacher and Rollman, 1993; Wilder-Smith, 2000). A potential criticism is its non-physiological nature and the mixed nerve fibre response it generally produces (dependent on stimulus characteristics), but this could in fact be an advantage in the surgical context, where nociception also affects multiple nerve populations. Patients were carefully instructed before inclusion into the study about the sensory testing paradigm and underwent several test runs to minimise variability. Possible sensitisation by electrical stimulation was curtailed by spacing testing and stopping on reaching the pain tolerance threshold, and the effect of reaction time minimised by slow ramping (0.1 $mA.s^{-1}$). Some effects might not have been detected due to insufficient sample size. Post hoc power testing shows that sample size was adequate to detect clinically relevant differences of at least one third for thresholds and morphine use. Regarding postoperative drug effects on thresholds, hangover from isoflurane or nitrous oxide is unlikely to be of significance, as subanaesthetic isoflurane concentrations have no effect on pain detection thresholds (Tomi et al., 1993), and the effects of nitrous oxide on the same continue for about 30 minutes after discontinuation (Ramsey et al., 1992). Opioids (e.g. morphine, fentanyl) have no or minimal direct effects on sensation or pain detection thresholds, with effects on pain tolerance thresholds being most marked for long and/or repeated stimulation (van der Burght et al., 1994; Liu et al., 1996). Diclofenac has smaller effects than opioids on threshold testing, but has been shown to raise electric and thermal tonic pain tolerance thresholds (Stacher et al., 1986). Effects due to either of the postoperative analgesics are unlikely to explain group threshold differences, however, due to their generally similar usage in all groups. The only exception is the markedly higher morphine use at 24 hours in the ketorolac group (vs. fentanyl) with major pain - here one would expect the ketorolac group to have a markedly higher threshold than the fentanyl group, but this is in fact not the case, tending to rule out morphine as an explanation of this difference. A further potential confounding factor could be differences in pain scores at the time of measure. To our knowledge, such effects have not been formally investigated to date, however, as pain scores were similar in the groups at all times after 6 hours postoperatively, this is unlikely to explain subsequent group differences in thresholds.

4.7. Postoperative sensory change and clinical pain measures

As in previous reports investigating both measures of sensory change and clinical pain after human surgery (Wilder-Smith et al., 1996; Wilder-Smith et al., 1998), the time course of the latter only partially and incompletely reflects that of the former. In this context, it appears that generalised changes in sensory processing affect clinical pain measures more

than do segmental changes. This is in conformity with recent reports as to serial aspects of nociceptive processing, particularly regarding pain intensity and affective aspects of the pain experience (Price, 2000). The relative lack of sensitivity of clinical pain measures to post-nociceptive changes in central sensory processing is furthermore hardly surprising in view of the accepted multifactorial origin and subjective nature of the individual experience of pain, and confirms the necessity of collecting direct measures of sensory change if the mechanisms of surgical nociception and its modulation are to be understood.

4.8. Implications for clinical practice and future research

A shift from symptom-based approaches to postoperative pain to mechanism-based management of postoperative nociception will only be achieved on the basis of a thorough understanding of the mechanisms involved. Our current results suggest that clinical pain measures alone are unlikely to prove adequate in this context as they only partially and incompletely reflect post-nociceptive changes in central nervous system processing, particularly at the spinal level. As nociceptive processing progresses rostrally in the central nervous system from the spinal level, the pathway ending in subjective and affective aspects of the pain experience involves processing in a serial, consecutive fashion, while the path to autonomic and metabolic arousal entails parallel, direct processing access (Price, 2000). Any outcome changes due to perioperative antinociceptive therapy, are, however, likely to be achieved via modulation of effects consequent to autonomic and metabolic arousal. Thus outcome-effective therapeutic intervention will have to be based upon an understanding and monitoring of more caudal changes in central nervous system sensory processing. This can only reliably be provided by direct measures of central sensory change. In view of this, and in view of the demonstrated complexity of central changes in sensory processing and its interaction with modulating factors such as pain and analgesia, we propose that future research - and clinical practice - needs to include measures of sensory change as provided, e.g., by quantitative sensory testing.

4.9. Conclusions

In conclusion, the present study shows that the basic response of central nervous system sensory processing to human surgery is one of segmental excitation followed later by generalised excitation, perhaps as the result of morphine analgesia ending and early acute supraspinal inhibitory controls fading. The presence of acute major pain preoperatively suppresses segmental sensitisation and subsequent generalised excitation, perhaps via the elicitation of acute supraspinal inhibitory mechanisms. Fentanyl analgesia too prevents segmental and subsequent generalised excitation, synergising with the effects of major preoperative pain. Ketorolac before surgery also blocks postoperative segmental excitation, but paradoxically does not prevent the appearance of late generalised excitation, perhaps due to antagonistic interactions with supraspinal inhibitory systems. These changes in central sensory processing are only partially manifest in clinical pain measures, suggesting the need to include direct measures of sensory change, e.g. via QST, in

future research and clinical practice concerning perioperative nociception. The interactions between endogenous and exogenous modulation of sensory change in the context of surgical nociception, and their relationship to clinical pain and surgical outcomes, require further detailed investigation.

Acknowledgements

We would like to thank Dr. Claude Senly for help with data collection.

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16. SUMMARY - TOWARDS A SYSTEMATIC ACCOUNT OF SURGICAL NEUROPLASTICITY

The six studies presented here represent a first systematic attempt to explore the post-operative neuroplasticity accompanying human surgery using a simple quantitative sensory testing (QST) paradigm, specifically adapted to the clinical context, involving thermal or electric stimulation of the skin. The studies allow first conclusions to be drawn regarding the time course of post-surgical neuroplasticity, its excitatory as well as inhibitory elements, the relative contributions made by spinal and supraspinal responses, and the effects of both intrinsic and extrinsic factors typically encountered in the surgical context. In addition, the present investigations permit further insights to be gained concerning the complex relationships between measures of the subjective pain experience and measures of the objective changes in central nervous system processing after surgical nociception. Finally, by virtue of the number of patients undergoing QST measurement in these studies, we can also draw conclusions as to the feasibility and practicability of performing such measures in the context of clinical routine.

The studies included in this section represent some 23000 individual threshold measures performed in over 200 patients for QST in the context of routine clinical surgery. In all of these studies, threshold measure variability during one QST session had to be less than 20%, otherwise the session had to be repeated, a condition which did not occur in any of the patients included in these studies. In addition, no patient refused to continue taking part in QST testing once they had been included in a study, demonstrating that relatively simple training for QST testing of this nature was adequate for our study purposes. Both thermal and electrical skin threshold testing are feasible in the clinical context, with electrical stimulation, the less physiological of the stimuli, proving to be less complicated to perform in practice and permitting a higher temporal and spatial density of measurements. The studies show that tonic/pain tolerance thresholds provide the best reflection of surgical nociceptive neuroplasticity and its modulation by a variety of clinically typical factors.

Taking all of these facts together, we would suggest that the QST paradigms we developed are practical for demonstrating nociceptive neuroplasticity in the clinical surgical environment. Two points need to be made in this context. Firstly, the *interindividual* variability of the thresholds proved to be relatively high, which is in keeping with other studies using QST (or neuroelectrophysiological methods) (1,2), and which is probably due to the highly variable nature of the genetic factors controlling nociceptive sensory processing (3). Secondly, the results obtained show the feasibility of separating spinal from supraspinal neuroplasticity by normalising thresholds close to surgery by reference (e.g. division) to thresholds distant from surgery.

16.1. Nature and Time Course of Post-Surgical Neuroplasticity

Using patients which are pain-free before surgery and who receive volatile anaesthesia without analgesic supplementation during surgery as the *control* (or comparator) *condition*, we have been able to demonstrate the following basic neuroplastic changes after surgery (Figure 1):

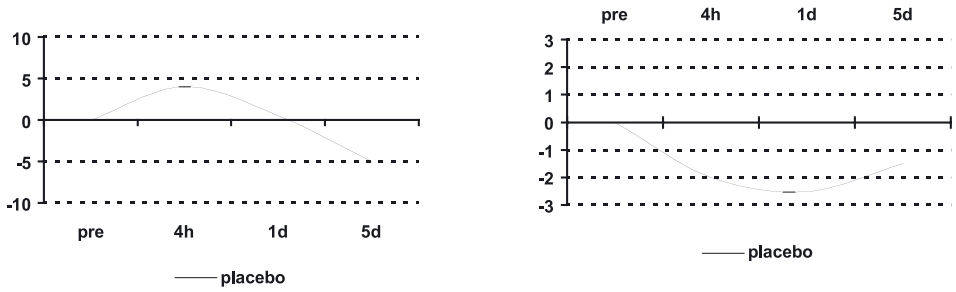

Figure 1: Surgical nociceptive neuroplasticity: no preoperative pain, no analgesic supplementation. Left: supraspinal neuroplasticity, change in absolute pain tolerance thresholds (mA). Right: spinal neuroplasticity, change in relative sensation thresholds (ratio).

16.1.1. Supraspinal (Generalised) Neuroplasticity

Up to 24 hours postoperatively, our patients showed threshold increases of up to 50%. These increases were most prominent for pain detection thresholds, maximal ca. 4 hours postoperatively and greater in the surgical dermatomes (4,5). Thresholds returned to preoperative baseline around 24 hours after surgery. By five days postoperatively, generalised hyperalgesia (i.e. thresholds reduce compared to preoperatively) was present. The preoperative threshold values had a significant effect on postoperative threshold values over the entire time course of the study.

16.1.2. Spinal (Segmental) Neuroplasticity

Our control patients show reductions in spinal thresholds (i.e. segmental, normalised vs. arm thresholds) throughout the postoperative period of up to ca. 50%. They were affected by preoperative threshold values only in the early postoperative period (4,5). These effects are only significant in non-nociceptive sensation thresholds, perhaps due to the known direct spinal effects of post-operative morphine analgesia on pain detection and pain tolerance thresholds, particularly in the presence of previous sensitisation (6).

16.1.3. Summary

In the absence of preoperative pain or analgesic supplementation, surgery results in long-lasting spinal excitation. Early postoperative supraspinal inhibitory neuroplasticity, maximal for C-fibre nociception, in traumatised dermatomes and at ca. 4 hours, is followed

later by generalised supraspinal excitatory neuroplasticity, still visible at day 5, and also maximal for C-fibre nociception and dermatomes subject to surgery. Our findings suggest that up to 24 hours postoperatively, supraspinal inhibition and morphine analgesia are able to suppress the supraspinal expression of excitatory neuroplasticity due to surgical nociception. Supraspinal spread of excitation then takes place, becoming visible as supraspinal hyperalgesia on day 5.

16.2a. How Does Analgesia Affect Postoperative Neuroplasticity?

We examined the effects of both neuraxial and systemic analgesia on post-surgical neuroplasticity in the absence of preoperative pain (Figure 2). The substances included in the studies were opioids (fentanyl, sufentanil), mixed opioid and monoamine agonists (tramadol), NMDA-blockers (ketamine, magnesium), and NSAIDs (ketorolac).

16.2a.1. Supraspinal (Generalised) Neuroplasticity

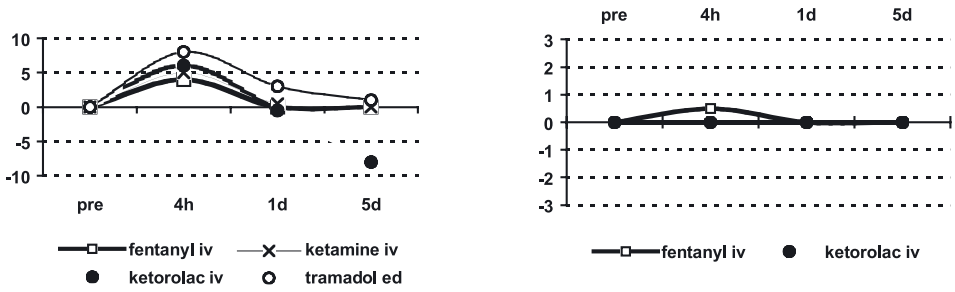

Figure 2: Surgical nociceptive neuroplasticity: no preoperative pain, but with analgesic supplementation. Left: supraspinal neuroplasticity, change in absolute pain tolerance thresholds (mA). Right: spinal neuroplasticity, change in relative sensation thresholds (ratio).

The pre- and intraoperative use of systemic fentanyl tends to result in synergistic increases in early postoperative increases in pain thresholds, and abolishes threshold reductions on day 5 (4,5,7). Systemic ketamine anaesthetic supplementation also raises early postoperative pain thresholds compared to preoperatively (more so than fentanyl), and is not associated with threshold reductions on day 5, although day 5 thresholds are lower absolutely than in fentanyl-complemented patients (7). The effects of systemic magnesium supplementation are similar to, but smaller than those of ketamine (7). Adding intravenous ketorolac to anaesthesia also results in increased early threshold rises, without, however, suppression of large late, day 5 decreases in pain thresholds (5). Postoperative epidural sufentanil (8) is associated with increased early (non-segmental) pain thresholds, while high doses of preoperative adjuvant epidural tramadol (9) result in long-lasting (up to 48 hours) postoperative pain threshold increases. The threshold changes in both epidural groups were determined far from the site of surgery and the seg-

ment of epidural catheter placement. In both epidural studies, pain thresholds were sensitive to excitatory drug effects. Comparing control (placebo) patients receiving approximately equipotent postoperative opioid intravenous PCA, the early postoperative increases in pain thresholds during PCA tramadol were smaller than those with PCA morphine (4,5,9).

16.2a.2. Spinal (Segmental) Neuroplasticity

All four systemic analgesic substances suppress postoperative reductions in spinal thresholds, with fentanyl showing a tendency to be associated with small rises in spinal thresholds (4,5,7). We did not test for segmental neuroplasticity with the epidural analgesics (8,9) due to the confounding effects of epidural local anaesthetic blockade.

16.2a.3. Summary

In the absence of preoperative pain, all analgesic anaesthetic supplements tested showed some synergistic increases in early postoperative supraspinal inhibitory neuroplasticity. The systemic substances investigated were similarly able to suppress postoperative spinal excitatory neuroplasticity. Despite suppressing spinal sensitisation, the NSAID ketorolac was not able to suppress late supraspinal hyperalgesia, being associated with significant late hyperalgesia comparable in degree to that seen without analgesic supplementation. However, both opioids and NMDA-antagonists did prevent subsequent late, day 5 postoperative supraspinal hyperalgesia, confirming predictions based on animal data that the impact of intraoperative analgesia (i.e. pre-emptive analgesia) on nociceptive neuroplasticity is much greater than that of postoperative analgesia. Based on the supposition that early postoperative hypoalgesia is dependent on the acute nociceptive input of surgery, the lesser early hypoalgesia in the control PCA tramadol patients as compared to the control PCA morphine patients is most likely due to the fact that the tramadol patients received epidural anaesthesia, whereas the morphine patients had ("non-analgesic") volatile general anaesthesia. This would again support the major importance of intraoperative antinociception in determining postoperative central neuroplasticity.

16.2b. How Does Preoperative Pain Affect Postoperative Neuroplasticity?

We found the presence of preoperative pain to be associated with significant neuroplasticity (10). Acute sciatic pain resulted in inhibitory neuroplasticity, while more chronic back pain was associated with excitatory neuroplasticity. Only for sciatica was there a significant, negative relationship between pain scores and pain thresholds. Regarding patients with acute preoperative pain and *not* receiving analgesic supplementation of anaesthesia for their surgery (5), we found the following changes in central sensory processing (Figure 3):

16.2b.1. Supraspinal (Generalised) Neuroplasticity

Patients with preoperative acute pain - and without intraoperative analgesia - had no late day 5 decreases in pain thresholds compared to preoperatively (5). The early increases in

pain thresholds were smaller than in patients without preoperative pain. Preoperative thresholds in these patients were significantly and negatively correlated to thresholds 1 and 5 days postoperatively.

16.2b.2. Spinal (Segmental) Neuroplasticity

Patients with preoperative acute pain and without intraoperative analgesia showed no decreases in spinal pain thresholds compared to preoperatively (5). At 24 hours postoperatively, spinal thresholds were increased compared vs. preoperatively. Preoperative spinal thresholds correlated significantly and negatively to postoperative ones throughout the postoperative period.

16.2b.3. Summary

Acute preoperative pain (e.g. sciatica) is associated with inhibitory supraspinal neuroplasticity preoperatively, and suppression of both spinal and subsequent supraspinal excitatory neuroplasticity postoperatively. It should be noted that patients with acute leg pain preoperatively had less early leg pain postoperatively.

16.2c. How Do Analgesia and Preoperative Pain Interact to Affect Postoperative Neuroplasticity?

Analgesic supplementation of anaesthesia with fentanyl as well as ketorolac was found to interact with the presence of acute pain preoperatively (5) (Figure 3):

16.2c.1. Supraspinal (Generalised) Neuroplasticity

Fentanyl supplementation in the presence of acute preoperative pain resulted in a tendency to greater early postoperative increases in pain thresholds as compared to patients without pain, while ketorolac supplementation was associated with smaller increases (5). As before, fentanyl abolished late (day 5) postoperative threshold decreases, while ketorolac supplementation was associated with large decreases in pain thresholds on day 5.

16.2c.2. Spinal (Segmental) Neuroplasticity

Spinal threshold decreases as compared to preoperative values were completely suppressed by fentanyl (5). Ketorolac supplementation was also associated with inhibition of spinal threshold decreases, albeit less so than in patients without analgesic supplementation or with fentanyl supplementation at 24 hours postoperatively (5).

16.2c.3. Summary

Adding fentanyl to anaesthesia generally interacts positively with the presence of preoperative acute pain in preventing excitatory neuroplasticity, both spinal and supraspinal,

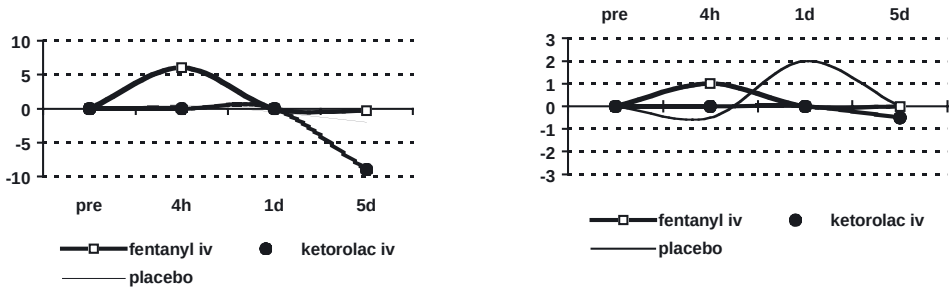

Figure 3: Surgical nociceptive neuroplasticity: with preoperative pain, and with analgesic supplementation. Left: supraspinal neuroplasticity, change in absolute pain tolerance thresholds (mA). Right: spinal neuroplasticity, change in relative sensation thresholds (ratio).

and in augmenting early postoperative supraspinal inhibition. Ketorolac anaesthetic supplementation in patients with acute preoperative pain has negative consequences in that early inhibitory supraspinal neuroplasticity is reduced and the blocking effect of acute preoperative pain on late (day 5) postoperative supraspinal hyperalgesia is abolished. It should be noted that in the presence of acute pain preoperatively, ketorolac-supplemented patients used one third more morphine by patient-controlled analgesia than did fentanyl-supplemented ones.

16.3. What Is the Relationship between Postoperative Neuroplasticity and Clinical Pain Measures?

Taking the studies presented here together (4,5,7-10), it is obvious that the relationship between various aspects of post-surgical central neuroplasticity and pain is a complex and multifactorial one. The neuroplastic changes seen in the various investigations discussed here are in general weakly and incompletely reflected by either pain scores or postoperative analgesia consumption. Thus measures of neuroplasticity and pain after surgery should be seen as providing complementary information, with the latter not being able to replace the former - or *vice versa*. Better understanding of the relationship between pain and neuroplasticity after surgery awaits further studies undertaking formal investigation of correlations between these factors as well as including larger patient numbers.

16.4. Implications: QST in Clinical Practice for Diagnosing Nociceptive Neuroplasticity

Both the advantages of using QST for demonstrating surgical nociceptive neuroplasticity as well as the disadvantages of *not* using such a technique support its introduction into clinical practice. As elucidated here, the advantages include that QST is relatively easy to establish in clinical practice, that it provides a defined, more objective measure of nociceptive surgical neuroplasticity, and that it is sensitive to factors clinically relevant for surgical nociception and its management. The price of *not* introducing QST for nociceptive neuroplasticity monitoring into clinical practice is that without such an endpoint, we have

no basis for achieving the shift from symptom-based to mechanism-based management strategies for surgical nociception. Without a measure of nociceptive neuroplasticity we have neither information on the mechanisms possibly involved nor a feedback measure for the therapeutic intervention instituted. Thus we would suggest that we have demonstrated that QST is feasible for demonstrating nociceptive neuroplasticity in clinical practice, that it provides information on the mechanisms involved in surgical nociception useful for both diagnostic and therapeutic purposes, and that it consequently warrants introduction into clinical research and practice for surgical nociception management.

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V

CONTROVERSIES AND CLINICAL APPLICATION

17. *Article* - The Pre-emptive Analgesia Debate Revisited

(Wilder-Smith OH. Pre-emptive analgesia and surgical pain. Prog Brain Res. 2000; 129: 505-24)

Pre-emptive analgesia and surgical pain

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Pre-emptive analgesia: concepts and background

The effective and consistent management of pain after surgery continues to be a therapeutic challenge (Zenz, 1997). In a recent survey of United Kingdom hospitals, significant pain was experienced after surgery by over 80% of the patients questioned (Bruster et al., 1994). About one third of these patients experienced postoperative pain that was continuously or almost continuously present for long periods of time. A United States survey of patients' concerns before surgery found postoperative pain to be the primary concern in almost 60% of those questioned, with approximately three-quarters of the respondents having experienced significant postoperative pain after previous surgery (Warfield and Kahn, 1995).

Bearing the hope of achieving significant improvements in the management of postoperative pain, the concept of pre-emptive analgesia was introduced in the late 1980s. The concept was founded upon an increasing body of animal research demonstrating central nervous system plasticity and sensitisation after nociception (Woolf, 1983; Woolf and Wall, 1986a; Woolf and Thompson, 1991), and was rapidly popularised by a number of pertinent editorials (Wall, 1988; McQuay and Dickenson, 1990; McQuay, 1992; Dahl and Kehlet, 1993; Bridenbaugh, 1994) and review articles (Woolf, 1989; Coderre et al., 1993; Woolf and Chong, 1993; McQuay, 1995) in the medical literature. In its original form, pre-emptive analgesia comprised two main postulates: firstly, that an analgesic intervention started before nociception would be more effective than the same intervention commenced afterwards; and secondly, that this advantageous effect would outlast the pharmacological duration of action of the analgesic concerned (see Jensen and Nikolajsen, 2000, this volume).

The presence of neuroplasticity is fundamental to the concept of pre-emptive analgesia. It is based upon findings in animal models (see: Gerber et al., 2000, this volume; Moore et al., 2000, this volume; Sandkühler et al., 2000, this volume; Svendsen et al., 2000, this volume) showing that nociceptive input to the central nervous system alters its subsequent function. These changes were initially shown to affect neurones in the dorsal horn of the spinal cord, but similar changes have now also been demonstrated to occur further up the synaptic chain of the central nervous system, e.g. in the thalamus (Gautron and Guilbaud, 1982; Guilbaud et al., 1989; see: Dostrovsky, 2000, this volume; Lenz et al., 2000, this volume) and cortex (see: Bromm et al., 2000, this volume; Casey, 2000, this volume; Flor, 2000, this volume). Early studies of nociceptive neuroplasticity, usually in non-intact (i.e. decerebrate or spinalised) preparations, elicited mainly excitatory changes (sensitisation) in central neuronal function that were most easily (but not exclusively) produced via C-fibre input. Signal summation was found to play a major role: temporal summation for non-inflamed tissue, spatial summation for inflamed or traumatised tissues. In the case of sensitisation, such summated input leads to long-lasting depolarisation

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which can significantly outlast the original nociceptive signal by seconds up to minutes and which can even start to occur spontaneously (wind-up, spontaneous pain).

The altered electrophysiological behaviour of the neurones concerned (i.e. synaptic long-term potentiation; Gerber et al., 2000, this volume; Sandkühler et al., 2000, this volume) spreads to adjacent neurones and results in reduced thresholds, increased responses to stimulation and after-discharging or spontaneous discharge. This central sensitisation expresses itself in the clinical symptoms of allodynia (previously non-painful stimuli are perceived as painful), hyperalgesia (increased pain sensation with a given nociceptive stimulus), wind-up (prolonged or spontaneous pain after stimulation) and increased size of the hypersensitive neuronal sensory fields (secondary hyperalgesia). Central sensitisation is the result of both posterior horn neuronal input facilitation as well as loss of inhibitory inputs, and must be distinguished from the primary hypersensitivity and hyperalgesia around a lesion due to sensitisation of peripheral nociceptors (Treede, 1995). The phenomenon of central sensitisation after nociception as seen in animal models is considered to play an important role in explaining the clinical manifestations of postoperative pain (cf. reviews cited above).

Biochemically, these changes in central neuronal function are mediated by the synaptic release of excitatory amino acid (e.g. glutamate, aspartate) — and also neuropeptide (e.g. substance P, neurokinin A) neurotransmitters and the subsequent binding to their membrane receptors (e.g. *N*-methyl-D-aspartate [NMDA] and tachykinin receptors) (e.g. Dickenson, 1995; Sandkühler et al., 2000, this volume). Activation of the NMDA receptor, dependent upon continuing NO production and the subsequent release of soluble GMP-cyclase (Meller and Gebhart, 1993), is necessary for the elicitation of central sensitisation (Woolf and Thompson, 1991; see, however, Hoheisel and Mense, 2000, this volume). Both NMDA and tachykinin receptor antagonists interfere with the electrophysiological consequences of nociceptive input at dorsal horn neurones as well as blocking the behavioural/clinical consequences of nociception. The release of excitatory amino acids (and/or tachykinins) results in slow synaptic dorsal horn potentials, the prerequisite for the electrophysiological neuronal membrane changes of central sensitisation, described above. Excitatory amino acid or tachykinin receptor activation (ligand gating) as well as membrane depolarisation (voltage gating) is accompanied by increased calcium entry into the neuronal cell bodies via calcium ionophores, thus raising cellular second-messenger (e.g. cGMP) and protein kinase C activity. The end result of these biochemical changes is not only positive feedback on the NMDA receptors but also the activated expression of early intermediate genes (e.g. c-*fos* or B-*jun*) regulating the production of modulatory substances such as the hyperalgesic dynorphin.

An early observation in animal models was that it is easier to prevent the establishment of central sensitisation (by providing analgesia, e.g. by morphine, before nociception occurred; pre-emptive analgesia) than to treat (suppress) it once established (Dickenson and Sullivan, 1986; Woolf and Wall, 1986b). In the animal models used, the dose of an analgesic — typically morphine — necessary to prevent electrophysiological central neuronal sensitisation was found to be much smaller than the dose necessary to suppress established sensitisation after nociceptive input. The electrophysiological advantages conferred by analgesic pre-emption were shown to outlast the pharmacological duration of action of the analgesic.

In the context of the important role central sensitisation is considered to play in postoperative pain, it is logical that the discovery of pre-emptive analgesia was rapidly followed by attempts to extend the concept into clinical — particularly surgical — practice. Extrapolating from the animal data at the time, the hypothesis for the human surgical pre-emptive analgesia studies undertaken in the early 1990s was that performing an analgesic intervention before surgery would result in a clearly better clinical pain outcome postoperatively than the same analgesic intervention initiated after surgery had started. It was further expected that the improvement in postoperative pain outcome would clearly outlast the pharmacological duration of action of the analgesic intervention used

Pre-emptive analgesia and surgical pain: the evidence of clinical studies

A large number of investigations of pre-emptive analgesia in the surgical context were undertaken in

the early 1990s. Unfortunately, by the mid-1990s, it was becoming clear that this first wave of studies was either unable to show any clinical effects of pre-emptive analgesia at all, or that the improvements in clinical pain outcomes were clinically disappointing, with only modest effects on postoperative pain measures or analgesic consumption. These modest effects were visible mainly using opioids (systemically and particularly neuraxially) and local anaesthetics. As discussed in a number of editorials and reviews published at the time (e.g. Woolf and Chong, 1993; Kehlet, 1994; McQuay, 1995; Wilder-Smith, 1995), problems in demonstrating clinically convincing effects of pre-emptive analgesia were initially considered in large part due to faults in clinical study design. Apart from basic points such as blinding, randomisation, prospectiveness and group sizes, these faults included issues such as contamination of the anaesthetic technique by other analgesic substances, absence of equality between the pre-emptive and post-emptive analgesic intervention, inadequacies in control states and lacking sensitivity of the clinical postoperative pain measures used. The question of how to match the analgesic intervention to the extent and duration of the nociception occurring during and after surgery was increasingly raised.

Since then a second series of clinical studies has been published, many with better designs. Some of the studies have addressed the question of adequately matching analgesia and nociception by studying genuine perioperative analgesia (i.e. for the entire duration of nociception) as opposed to only bolus analgesic interventions (e.g. Gottschalk et al., 1998; Likar et al., 1998). The results of a literature survey for this 'second wave' of pre-emptive analgesia studies are summarised in Tables 1 and 2. The survey was performed using MEDLINE and the keyword 'pre-emptive analgesia and surgery', and includes only randomised, controlled and prospective studies with valid design (i.e. pre- and post-nociceptive interventions).

As can be seen from the studies detailed in Tables 1 and 2, improvements in study design have been followed by more success in demonstrating effects of pre-emptive analgesia for opioids, ketamine (a non-competitive NMDA receptor antagonist) and local anaesthesia. It should be noted that in the positive studies (Table 1), the improvements in clinical pain outcomes achieved are generally small and of short duration. Studies with adequate design but not finding any effect also continue to be published. Due to the well-known publication bias against negative studies, it remains difficult to establish a true final weight of evidence for or against clinically relevant pre-emptive analgesia. On the present balance of evidence, we would suggest that while there is evidence that opioids, NMDA-antagonists and local anaesthesia have pre-emptive analgesia effects, these effects are modest and of limited clinical significance. There is a suggestion that the clinical efficacy of analgesic pre-emption may improve with better matching between analgesic intervention and nociceptive input.

Redefining the pre-emptive analgesia problem

Why is there such a discrepancy between the success of pre-emptive analgesia in the experimental animal model and in the clinical surgery patient? In looking more closely at the two models and at their commonalties and similarities we would suggest that three closely linked problems are operating: (1) the problem of extrapolation from experimental to clinical; (2) the problem of clinical study design; (3) the problem of how to measure pain outcomes.

The problem of *extrapolation* rests upon the fundamental differences between experimental and surgical pain models. *Firstly*, the duration and magnitude of, and number of modalities involved in surgical nociception are far greater than for experimental nociception models. In surgery, nociceptive input continues in the presence of extensively chemically sensitised traumatised tissues, which is often not the case in animal models, particularly the early ones. *Secondly*, a large proportion of animal models involve non-intact (i.e. spinalised or decerebrate) preparations — again, particularly earlier models — while surgical models are intact with regard to their central nervous system. Non-intact animal models will therefore neither reflect the integral effects of nociception on a whole central nervous system, nor will they be able to demonstrate the *responses* with which an intact central nervous system defends itself against nociceptive inputs. These defences will include both neuronally (e.g. descending inhibitory controls; see Sandkühler et al., 2000, this volume, and Svendsen et al., 2000, this volume) and hormon-

TABLE 1

Summary of clinical studies 1992–1999 showing pre-emptive analgesia effect

Study	Design			Analgesic intervention			Surgery
	Analgesia: pre + post present?	Analgesia: pre = post?	Comments	Type			
Chia et al., 1999	yes	yes		IV	short infusion	dextromethorphan 5 mg/kg	major abdo surgery
Wu et al., 1999	yes	yes	also: placebo control	IM	bolus	dextromethorphan 40 mg	laparoscopic cholecystect
Ke et al., 1998	yes	yes	also: placebo control	II	single	0.5% bupivacaine	diagn gynae laparoscopy
Kundra et al., 1998	yes	yes		caudal ED	single	bupivacaine, morph 0.02 mg/kg	herniorraphy
Likar et al., 1998	periop vs. postop		placebo control	IV	infusion	ketoprofen 100 mg, then 12 mg/h	gynae surgery
Gottschalk et al., 1998	periop vs. postop			ED	infusion	bupivacaine, fentanyl	radical prostatectomy
Griffin et al., 1997	yes	yes	small groups (2 × 19)	IV	short infusion	alfentanil 70 μg/kg	abdo hysterectomy
Kundra et al., 1997	yes	yes	small groups (2 × 15)	ED	bolus	morphine 3 mg	lumbar laminectomy
Fu et al., 1997	yes	pre > post		IV	infusion	ketamine	abdo surgery
Choe et al., 1997	yes	yes		ED	bolus	ketamine 60 mg morphine 2 mg	mixed surgery
Romej et al., 1996	yes	yes		PR	single	paracetamol 20 mg/kg	tonsillectomy
Pasqualucci et al., 1996	yes	yes	cont: placebo, pre + post	IP	single	bupivacaine	laparoscopic cholecystect
Rockemann et al., 1996	yes	yes	placebo control	balanced analgesia		diclofenac 75 mg metamizol 1 g ED mepivacaine ED morphine 1 mg	major abdominal surgery
Richmond et al., 1993	yes	yes	IM control	IV	single	morphine 10 mg	abdominal hysterectomy
Katz et al., 1992	yes	yes	small groups (2 × 15)	ED	single	fentanyl 4 μg/kg	thoracotomy

TABLE 1 (continued)

Study	Pain measures and their improvement pre vs. post						Comments
	Pain intensity	Improved? When?	Analgesic consumption	Improved? When?	Others	Improved? When?	
Chia et al., 1999	VAS (rest)	↔0–3 d	PCA morphine	↓d1,2	pat satisfact side effects	↔	
	VAS (exert)	↔0–3 d				↔	
Wu et al., 1999	worst VAS	↓	IM pethidine on demand	↓48 h (total)	TFA bed rest	↑	worst: placebo
						↔	
Ke et al., 1998	MPPIS	↓24 h	suppl. analgesia use	↔	TFA	post = placebo	
Kundra et al., 1998	OPS	↓0.5, 4, 8 h	nurse demand morphine	↓24 h (total)	TFA side effects	↑	children
						↔	
Likar et al., 1998	VAS (rest)	↓24 h	PCA piritramide	↔	TFA	↑	PCA piritram: pre < placebo
	VAS (exert)	↓24 h					
Gottschalk et al., 1998	VAS	↓hosp. 9.5 wk	ED!	–	activity	↑3.5 wk	
		↔3.5, 5.5 wk				↔5.5, 9.5 wk	
Griffin et al., 1997	VAS (rest)	↔0–72 h	PCA morphine	↓48–72 h			
	VAS (exert)	↔0–72 h					
Kundra et al., 1997	VAS	↓8 h	PCA morphine	↓24 h (total)	TFA	↑	↓sedation, PONV
Fu et al., 1997	VAS	↔d1,2	PCA morphine	↓d1,2			
Choe et al., 1997	–	–	no. receiving sup. morphine	↓	T1–2A	↑	
Romej et al., 1996	FLACC	↓30 min	nurse demand morphine	↓24 h (total)	RMPO OI (time, total)	↓	children
		↓240 min				↔	
Pasqualucci et al., 1996	VAS	↓24 h	suppl. analgesia	↓24 h (total)	blood glucose, cortisol	↓at 3 h	
Rockemann et al., 1996	VAS	↔0–5 d	PCA morphine	↓d2, d5 (total)			
Richmond et al., 1993	VAS	?	PCA morphine	↓	relative pain thresholds	↓24 h	
Katz et al., 1992	VAS	↓6 h	PCA morphine	?			

Abbreviations: IV = intravenous; IM = intramuscular; II = incisional infiltration; ED = epidural; PR = per rectum; VAS = visual analogue score; MPPIS = McGill present pain intensity score; OPS = objective pain score; FLACC = faces, legs, activity, cry, consolability; PCA = patient-controlled analgesia; TFA = time to first analgesia demand; T1–2A = time between first and second analgesia demand; RMPO = rescue morphine directly postoperatively; OI = oral intake.

TABLE 2

Summary of clinical studies 1992–1999 showing no pre-emptive analgesia effect

Study	Design			Analgesic intervention			Surgery
	Analgesia: pre + post present?	Analgesia: pre = post?	Comments	Type			
Heinke and Grimm, 1999	yes	pre > post	placebo control	IV	bolus ± infusion	ketamine 0.5 mg/kg ± 10 μg kg^{-1} min^{-1}	gynae laparotomy
Campbell et al., 1998	yes	yes	one session	LAB IV IV	single	bupivacaine 0.5% tenoxicam alfentanil	bilateral lower 3rd molar extraction
Kucuk et al., 1998	yes	yes	power calculation!	ED	bolus	ketamine 60 mg	upper abdominal
Bourget et al., 1997	yes	yes	$N = 112$	II	single	bupivacaine 0.25%	elective abdo laparotomy
Likar et al., 1997	yes	yes		IV	short infusion	ketoprofen 2 mg/kg	gynae procedures
Ho et al., 1997	yes	yes	$N = 51$	caudal ED	single	0.25% bupivacaine	hernia, circumcision, orchidopexy
Aguilar et al., 1996	yes	yes	placebo control	thoracic ED	single	0.5% bupivacaine	thoracotomy
Fassoulaki et al., 1995	yes	yes		IV	bolus	fentanyl 10 μg/kg sufentanil 1 μg/kg	abdominal hysterectomy

Study	Pain measures and their improvement pre vs. post						Comments
	Pain intensity	Improved? When?	Analgesic consumption	Improved? When?	Others	Improved? When?	
Heinke and Grimm, 1999	VAS	↔	IM opioids	↔			alfentanil intraop
Campbell et al., 1998	VAS MPQ	↔6 h, 1, 3, 6 d ↔1 d	–	–			
Kucuk et al., 1998	–		ED pethidine	↔d1,2 (total)			
Bourget et al., 1997	VRS	↔3 d	IM morphine	↔3 d			
Likar et al., 1997	VAS	↔24 h	nurse demand piritramide	↔24 h	TFA	↔	
Ho et al., 1997	FPS	↔ postop, home	analgesic supplement	↔			children
Aguilar et al., 1996	VAS (rest) VAS (cough) VAS (move)	↔48 h ↔48 h ↔48 h	PCEA bupiv 0.125% fentanyl 6 μg/ml	↔48 h			alfentanil intraop, ED fentanyl at operation end
Fassoulaki et al., 1995	VAS VRS	↑30, 120 min ↑30, 120 min	nurse demand opioids	↔24 h (total)	TFA	↔	

Abbreviations: IV = intravenous; LAB = local anaesthetic block; ED = epidural; II = incisional infiltration; VAS = visual analogue score; MPS = McGill pain questionnaire; VRS = verbal rating score; FPS = faces pain scale; IM = intramuscular; PCEA = patient-controlled epidural analgesia; TFA = time to first analgesia demand.

ally (e.g. stress-induced analgesia) mediated central nervous system responses to nociceptive input (Le Bars et al., 1979, 1992; Kelly, 1986; Termann et al., 1986). It is of interest that intact animal models using longer-lasting nociceptive inputs show pre-emptive analgesia results much closer to the modest results achieved in human surgical pre-emptive analgesia studies (e.g. Jayaram et al., 1995; Fletcher et al., 1996) than those involving non-intact preparations.

The main difficulties with *clinical study design* involve questions of standardisation. Standardising surgery is notoriously difficult, but should be attempted, both by the use of agreed defined surgical protocols and by limiting the number of surgeons as far as possible (one surgeon is ideal!). Standardisation of the patients is far more difficult, as the variability of patient's responses to pain and nociception is generally underestimated and — so far — not amenable to selection or prediction. Animal studies of the genetically inherited component in the responses to pain (e.g. sensitivity, inhibitory controls) have shown a large variability in this area (Lutfy et al., 1994; Mogil et al., 1995; Sternberg and Liebeskind, 1995; Kest et al., 1999). Thus study size must always be adequate to cope with this variability of pain sensitivity and responses, albeit tempered by the desire to demonstrate truly clinically relevant effects. Other important design features include the equality of the pre- and post-nociceptive analgesic interventions as well as an adequate match between nociception and analgesic intervention regarding intensity, duration and sensory modalities involved. The latter feature was a particular problem with earlier pre-emptive analgesia studies: a single bolus of morphine may well adequately cover the nociception of a brief electrical C-fibre stimulus, but it is unlikely to cover the nociception associated with an abdominal laparotomy lasting several hours. Included in this problem is the question of when nociception ends; again, for a brief electrical C-fibre nociceptive stimulus this is easy to define, but when does surgical nociception really end? This problem will obviously also affect the definition of the post-emptive analgesia comparison state.

The final problem concerns the question of *measuring pain and its outcomes*. A major difference between experimental animal and clinical human pain studies is the difference in pain measures used. Clinical, e.g. post-surgical, pain is a subjective phenomenon, directly accessible only to the conscious person experiencing it. This experience of pain is influenced by a multitude of factors apart from the nociception causing it and therefore bears no direct, linear relationship to the nociceptive event causing it. In intact animal pain studies, we have to rely on indirect behavioural correlates of the pain experience (e.g. tail flick latency, hot plate latencies, etc.) as the animal cannot communicate the pain in a more direct fashion. It must be clear that these behavioural pain measures are only surrogate measures which neither measure the pain experience nor the characteristics of the nociceptive event directly. The electrophysiological measures used in non-intact animal pain studies are even further removed from the subjective pain experience of clinical, post-surgical pain. They may, however, encode more information about the original nociceptive event and the damage or stress it is causing to the body than behavioural measures. Thus the comparison of behavioural or electrophysiological results from animal research with the results of clinical pain measures in humans will always be difficult.

The above-mentioned difficulties pertain to human pain research, too. Subjective clinical pain measures such as pain intensity scales or postoperative analgesia use tell us different things than the objective measures of psychophysical (e.g. pain thresholds) or electrophysiological (e.g. nociceptive flexion reflexes) testing do. Despite the fact that clinical pain measures such as visual analogue pain intensity scales (VAS) or postoperative patient-controlled analgesia (PCA) consumption have been used for quite some time in pain research, we are still unsure as to what they really tell us and how they behave under different circumstances. This is illustrated, e.g. by the quantal — *not* linear — dose–effect relationship between titrated dose of alfentanil given intravenously and postoperative pain relief (Fig. 1) (Tverskoy et al., 1996). The non-linear relationship between dose of opioid given and degree of (subjective) pain relief obtained is a reflection of the multifactorial nature of the subjective pain experience already discussed, and specified in the original IASP definition of pain. In view of the multi-aetiological nature of the subjective, clinical pain experience, it is unrealistic to expect clinical pain to correlate closely with the lower-order func-

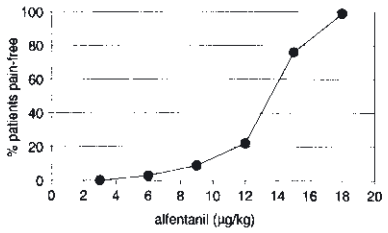

Fig. 1. Figure modified after Tverskoy et al. (1996) showing the cumulative frequency distribution curve for the *complete* relief of spontaneous postoperative pain by 3 µg/kg intravenous increments of alfentanil, given at 5-min intervals.

tional changes in the central nervous system function described in the original animal studies of neuroplasticity after nociception and pre-emptive analgesia. If we are to investigate the human correlates of the pre-emptive analgesia found in animal studies, we must study similar-order phenomena in humans, namely changes in objective psychophysical or electrophysiological measures reflecting altered central nervous system function after nociception. Indeed, if changes in the analgesic management of surgery are to have effects on long-term medical outcome, it should be of particular interest to study these objective measure of altered sensory processing, as they may reflect the damage done to the body by nociception — and its modulation — much more closely than subjective clinical pain measures could.

Towards a relevant human study design for pre-emptive analgesia

The pre-emptive effect of analgesia in animal studies is primarily defined in terms of altered central nervous system function. These alterations have mainly been described as affecting sensory and lower-order (spinal, thalamic) central nervous system processing. In order to effectively study pre-emptive analgesia in the human context, it therefore appears logical to study alterations in central nervous system sensory processing as a result of surgical nociception, and how this can be modulated by analgesic intervention. *It is at this level that the reality or not of pre-emptive analgesia should first be established.* The relationship between altered central nervous system processing and subjective, clinical pain measures or long-term medical outcomes can then be established in a second step.

If studies of human pre-emptive analgesia and surgery are to be performed in the clinical context, the techniques involved need to be simple, valid, easily performed and not too time-consuming. Psychophysical measures such as pain or sensation thresholds offer such a technique. With adequate training of experimenter and subject together with good protocol design and standardisation, they are simple, reproducible, reliable and not too time-consuming in use, and have been well-validated as reflecting central nervous system sensory processing and its alterations (Rollmann and Harris, 1987; Lautenbacher and Rollman, 1993; Arendt-Nielsen et al., 1995; Wilder-Smith et al., 1996, 1998). In order to obtain comprehensive answers about alterations in sensory processing after surgery, thresholds need to be measured at multiple sites. Ideally, thresholds should be measured on the wound (primary hyperalgesia), near the wound (ca. 10–15 cm from the wound; secondary hyperalgesia), as well distant to the site of surgery (to detect generalised effects such as descending inhibition or stress-induced analgesia). Measuring multiple sensory modalities (i.e. sensation, pain detection, pain tolerance thresholds) and multiple stimulation modalities (i.e. mechanical, electric, thermal) increases the understanding of the sensory changes involved (see also Treede and Magerl, 2000, this volume). It should also be remembered that direct nerve stimulation will give different answers than dermatomal stimulation. All the psychophysical tests mentioned so far will only involve superficial, cutaneous structures; methods for testing deep (e.g. muscle (see Hoheisel and Mense, 2000, this volume)) or visceral structures remain experimental and difficult to transfer to the clinical context for the time being (Cervero, 1995; Gavrilov et al., 1996; Bajaj et al., 1999).

The psychophysical measures under discussion need to be embedded in a well-conceived and well-standardised design. The analgesic intervention should be well-matched to the nociception concerned to make the results relevant. Thought should be given to making the study feasible in the clinical context, otherwise too many data points will be missed. In order to enable objective, psychophysical and subjective clinical pain measures to be compared or

correlated, they should be measured simultaneously. If several clinical pain measures are measured (e.g. pain VAS and PCA morphine use), which is the primary and which is the secondary endpoint must be determined (i.e. if PCA morphine use is to be the measure, aim for similar VAS scores targets in all patients). It is desirable to extend the period of study for as long as feasible, particularly if effects on medical outcome are to be investigated.

Sensory processing after surgery: defining the changes

In the last decade, a number of studies have been performed to investigate changes in sensory processing due to surgical nociception and how these can be modulated by analgesic interventions. The findings of these selected studies, both clinical human and animal, are summarised in Table 3. From the results of the studies we will try to answer the following pertinent questions: (1) what are the changes in sensory processing after surgery? (2) can central sensitisation be detected after surgery? (3) how are the changes in sensory processing affected by analgesic intervention? (4) what other factors affect post-surgical sensory change?

Mechanical pain thresholds measured distant to the surgical wound are either unaltered or moderately decreased in the studies concerned (Lascelles et al., 1995, 1997, 1998; Welsh and Nolan, 1995; Moiniche et al., 1997). In none of the studies cited were non-nociceptive mechanical thresholds measured distant to surgery. When present, distant hyperalgesia is visible within the first 24 h postoperatively and is suppressed by opioid pre-emptive analgesia. Mechanical hyperalgesia close to the wound (secondary hyperalgesia), considered to reflect central sensitisation (see Treede and Magerl, 2000, this volume), is more pronounced and of longer duration, appearing to be present up to 4–5 days postoperatively (Richmond et al., 1993; Moiniche et al., 1997; Stubhaug, 1997) and gone by 8 days (Moiniche et al., 1997). The area of secondary hypersensitivity has been shown to be reduced by ketamine pre-emptive analgesia (Stubhaug, 1997). Wound hyperalgesia (primary hyperalgesia) is considered to reflect both peripheral nociceptor and central nervous sensitisation. As expected, mechanical pain thresholds at the surgical incision are lower postoperatively, with such hyperalgesia being reduced — but not abolished — by opioid pre-emption (Dahl et al., 1990; Lascelles et al., 1997, 1998; Moiniche et al., 1997). One study has shown wound hyperalgesia to be gone at 8 days postoperatively (Moiniche et al., 1997).

Only one clinical animal study has investigated thermal hyperalgesia after surgery (Welsh and Nolan, 1995), demonstrating early (<1 h postoperatively) distant hyperalgesia, reduced by opioid pre-emption, after laparotomy.

Electrical sensory thresholds are particularly easy to use in the clinical context and have been extensively validated experimentally (Rollmann and Harris, 1987; Lautenbacher and Rollman, 1993). Electrical stimulation has the additional advantage of producing multimodal sensory stimulation, stimulating both large and small nerve fibres, which may be particularly relevant to the multimodal sensory input resulting from surgery (Arendt-Nielsen et al., 1994). We have used electrical stimulation to study postoperative sensory change both in back surgery (prolapsed intervertebral discs) and in abdominal surgery (hysterectomies) (Wilder-Smith et al., 1996, 1998). Compared to preoperative values, dermatomal electric stimulation distant to the surgical incision shows early (<24 h postoperatively) increases in both nociceptive and non-nociceptive thresholds, increased by pre-emptive analgesia (Figs. 2 and 3). Closer to the wound (secondary hyperalgesia) the absolute nociceptive and non-nociceptive thresholds also show early increases (1–24 h postoperatively), with a tendency to be higher than at sites distant to surgery (Figs. 2 and 3). Again, this hypoalgesia and hyposensitivity is augmented by opioid pre-emption. It is unlikely to be explained solely by postoperative morphine analgesia, as it is also visible for non-nociceptive thresholds which are not directly affected by opioids (Van der Burght et al., 1994). If, however, thresholds close to the wound *relative* to the distant thresholds are calculated (i.e. for a given time: threshold close to wound divided by threshold distant from wound) to remove any generalised inhibitory effects, these relative thresholds close to the wound show an early (1–24 h postoperatively) reduction compared to preoperatively in the absence of opioid pre-emption (Fig. 4), suggesting central neuronal sensitisation. This sensitisation is visible in

TABLE 3

Summary of studies investigating sensory change after surgery to date

Study	Type of surgery	Type of stimulation	Stimulation endpoint	Absolute or relative	Preop measures?	On wound (1°) (post vs. preop)	When postop
HUMAN							
Richmond et al., 1993	hysterectomy	M (vF)	S, PD	REL to forearm	no	–	–
Tverskoy et al., 1994	hysterectomy	M	PD	ABS	no	↓↓(NPE) ↓(PE)	24, 48 h
Moiniche et al., 1997	hysterectomy	M (P)	PD	ABS	yes	↓↓	4, 6 h, 1, 4 d
						↔	8 d
Stubhaug, 1997	renal	M (vF)	S, PD, TS	ABS	yes	–	–
Lund et al., 1990	hysterectomy	E (D)	S	ABS	yes	–	–
Dahl et al., 1992	gynae lap	E (N)	PT	ABS	yes	–	–
Dahl et al., 1990	hernia	M (P)	PD	ABS	yes	↓	?
Wilder-Smith et al., 1996	back (herniated disc)	E (D)	S, PD, PT	ABS REL to arm	yes	–	–
Wilder-Smith et al., 1998	hysterectomy	E (D)	S, PD, PT	ABS REL to arm	yes	–	–
Wilder-Smith et al., 1999a	hysterectomy	E (D)	S, PT	ABS	yes	–	–

Study	Near wound (2°) (post vs. preop)	When postop	Distant to wound (post vs. preop)	When postop	Preempt analgesia	Postop analgesia
HUMAN						
Richmond et al., 1993	REL: ↓(NPE) ↓(PE)	24, 48 h	?	–	morphine	PCA morphine
Tverskoy et al., 1994	–	–	–	–	fentanyl ketamine	IV pethidine
Moiniche et al., 1997	↓	4, 6 h, 1, 4 d	↔	4, 6 h, 1, 4 d	–	IM morphine
	↔	8 d	↔	8 d		
Stubhaug, 1997	↓(PE: ↓area)	1, 3, 7 d	–	–	ketamine	PCA morphine
Dahl et al., 1990	–	–	↑	48 h	–	IM morphine
Dahl et al., 1992	–	–	↓	48–96 h	–	IM morphine
Dahl et al., 1990	–	–	–	–	–	IM morphine
Wilder-Smith et al., 1996	ABS: ↑(NPE) ↑↑(PE)	1, 2, 4, 6 h	ABS: ↑(PE)[1]/↓(NPE)[2]	1–4 h[1]/5 d[2] rest	fentanyl	PCA morphine
	ABS: ↔(NPE/PE)	1, 5 d	ABS: ↔ (PE/NPE)			
	REL: ↓(NPE)	4, 6 h, 5 d	REL: N/A			
	REL: ↔(PE)	1 h–5 d				
Wilder-Smith et al., 1998	ABS: ↑↑	4 h, 1 d	ABS: ↑	4 h	fentanyl ketamine magnes.	PCA morphine
	REL: ↔	1 h–5 d	REL: N/A			
Wilder-Smith et al., 1999a	↔	2, 4 d, 1 m	↓	4 d	–	PCA mo/tram

TABLE 3 (continued)

Study	Type of surgery	Type of stimulation	Stimulation endpoint	Absolute or relative	Preop measures?	On wound (1°) (post vs. preop)	When postop
ANIMAL							
Welsh and Nolan, 1995	sheep laparotomy	M (P) T	PT	ABS	yes	–	–
Lascelles et al., 1995	rat ovario-hysterectomy	M (P)	PD	ABS	yes	–	–
Lascelles et al., 1997	dog ovario-hysterectomy	M (P)	PD	ABS	yes	↓↓(NPE) ↓(PE)	8, 12, 20 h
Lascelles et al., 1998	dog ovario-hysterectomy	M (P)	PD	ABS	yes	↓↓(NPE) ↓(PE)	8, 12, 20 h

Study	Near wound (2°) (post vs. preop)	When postop	Distant to wound (post vs. preop)	When postop	Preempt analgesia	Postop analgesia
ANIMAL						
Welsh and Nolan, 1995	–	–	M: ↔ T: ↓↓(NPE) ↓(PE)	0–120 min 45, 60 min	carprofen	–
Lascelles et al., 1995	–	–	↓(NPE) ↔(PE)	2.5–6.5 h	pethidine	–
Lascelles et al., 1997	–	–	↓(NPE) ↔(PE)	12, 20 h 8, 12, 20 h	pethidine	–
Lascelles et al., 1998	–	–	↓(NPE) ↔(PE)	12, 20 h 8, 12, 20 h	carprofen	–

Abbreviations: M = mechanical; P = pressure; vF = von Frey hair; E = electrical; N = direct nerve stimulation; D = dermatomal stimulation; T = thermal; S = sensation threshold; PD = pain detection threshold; PT = pain tolerance threshold; ABS = absolute; REL = relative threshold; NPE = no pre-emptive analgesia; PE = pre-emptive analgesia; N/A = not applicable; h = hours; d = days; m = months; IM = intramuscular; PCA = patient-controlled analgesia; magnes. = magnesium sulphate.
Notes: [1] on arm [2] in leg dermatome most affected by herniated disc prolapse.

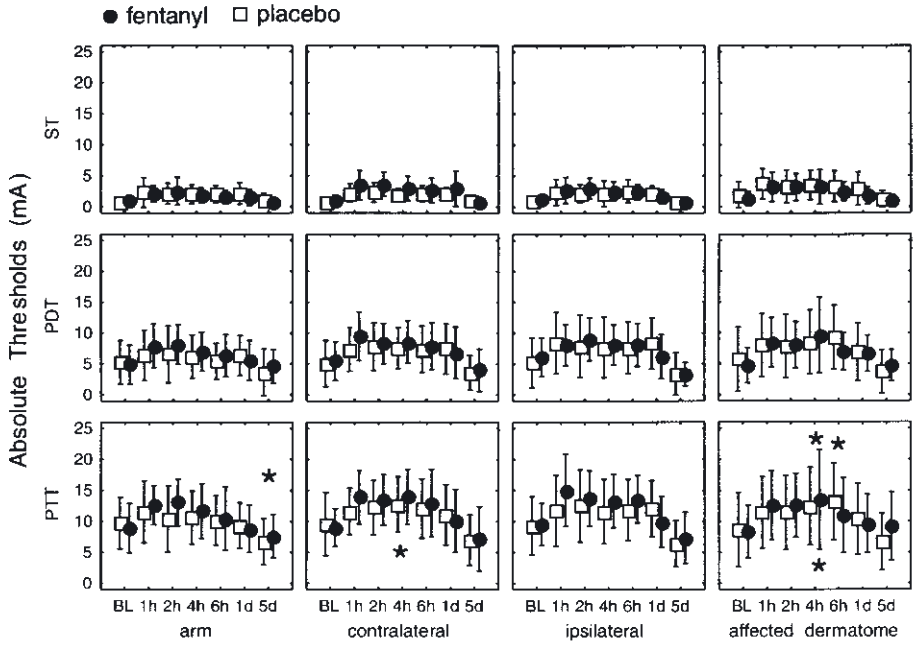

Fig. 2. Absolute thresholds by electric skin stimulation in mA (means, standard deviations) at preoperative baseline (*BL*) and 1, 2, 4, 6 and 24 h and 5 days after surgery for herniated intervertebral discs (after Wilder-Smith et al., 1996). Anaesthesia: isoflurane/nitrous oxide/oxygen ± 3 μg/kg fentanyl i.v. before intubation. Sites of measure: arm, contralateral and ipsilateral to the back incision, and the dermatome of the nerve most affected by disc prolapse. Thresholds measured: sensation (*ST*), pain detection (*PDT*) and pain tolerance (*PTT*). Significant overall statistics (repeated measures ANOVA for drug, threshold site, threshold type and time): fentanyl > placebo; PTT > PDT > ST; arm < contralateral = ipsilateral = affected dermatome; 4 h > BL. Significances ($p < 0.05$) for specific times, sites and measures are marked on the graph: * = significant vs. BL, with values for placebo marked above and for fentanyl marked below the curves.

non-nociceptive thresholds not directly affected by opioid analgesia. Central sensitisation is no longer visible in the presence of analgesic supplementation by opioids or NMDA antagonists (Figs. 4 and 5).

Using another technique, namely directly electrically stimulating a nerve distant to the site of surgery, but innervated by spinal cord segments convergently involved in the surgery, another group (Dahl et al., 1992) has also been able to demonstrate hyperalgesia and central neuronal sensitisation 48–96 h postoperatively.

Studies of the process whereby pain becomes chronic (see Jensen and Nikolajsen, 2000, this volume) suggest that a central nervous system already sensitised by preceding nociception, e.g. ischemic pain before limb amputation (Bach et al., 1988), is more vulnerable to further neuroplastic change and its chronification. An advantage of studying sensory change after surgery for prolapsed intervertebral discs is that many of these patients suffer pain preoperatively and may thus show central nervous system sensitisation preoperatively. In a study of preoperative sensory change in patients scheduled for herniated disc surgery (Wilder-Smith et al., 1999b), we were able to demonstrate that patients with moderate to severe preoperative pain (VAS > 5) showed pain thresholds significantly different from those without preoperative pain (Fig. 6). Of note is the fact that

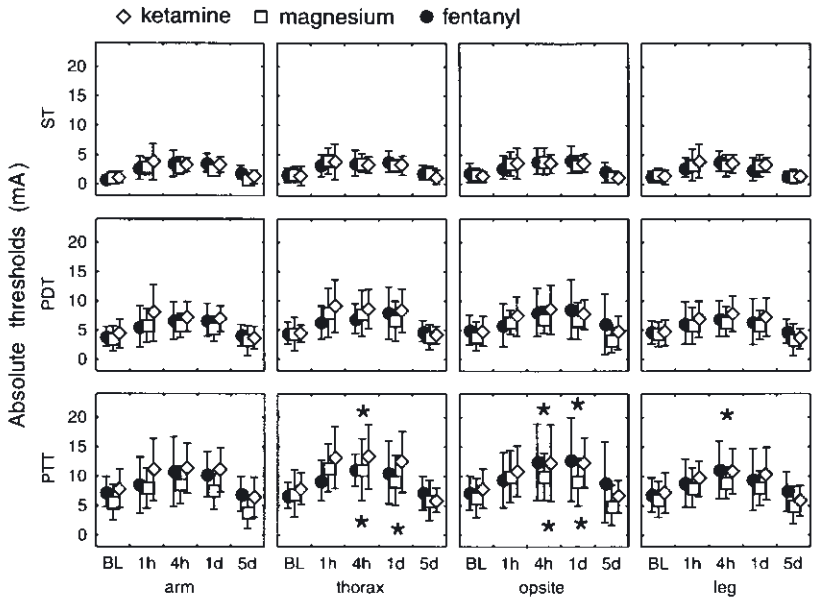

Fig. 3. Absolute thresholds by electric skin stimulation in mA (means, standard deviations) at preoperative baseline and 1, 4 and 24 h and 5 days after surgery for abdominal hysterectomy (after Wilder-Smith et al., 1998). Anaesthesia: isoflurane/nitrous oxide/oxygen supplemented by either fentanyl, magnesium or ketamine. Sites of measure: arm, operation site, thorax and upper thigh. Thresholds measured: sensation (*ST*), pain detection (*PDT*) and pain tolerance (*PTT*). Significant overall statistics (repeated measures ANOVA for drug, threshold site, threshold type and time): PTT > PDT > ST; 1–24 h > BL. There is no significant effect by drug group. Significances ($p < 0.05$) for specific times, sites and measures are marked on the graph: * = significant vs. BL, with values for fentanyl marked above and for ketamine marked below the curves.

while somatic pain (i.e. pain in the back) was associated with lowered pain tolerance thresholds to electrical stimulation — congruent with central sensitisation — pain of neuropathic quality (i.e. radiating down the leg) was associated with *increased* pain thresholds, suggesting either inhibitory processes or nerve dysfunction. Interestingly, in the study of back surgery mentioned above (Wilder-Smith et al., 1996), the patients not receiving analgesic supplementation for anaesthesia not only continued showing lowered *relative* thresholds compared to preoperatively in the dermatome most affected by disc prolapse 5 days postoperatively, they also had lower *absolute* electric pain tolerance thresholds on day 5 (Figs. 2 and 4).

It should be noted in this context that different sensory modalities of measurement may give somewhat differing results, e.g. mechanical thresholds may be less sensitive to descending inhibition than thermal or electrical measures (cf. also, e.g. Lautenbacher and Rollman, 1993).

In summary, to date there is evidence for the following central changes in sensory processing following surgical nociception:

(1) distant from the wound: early hypoalgesia (up to ca. 12–24 h postoperatively), increased by pre-emptive analgesia, affecting both nociceptive and non-nociceptive sensory processing; later modest hyperalgesia possible (up to 4–7 d postoperatively), decreased or abolished by pre-emptive analgesia, probably increased by preoperative sensory sensitisation (preoperative pain);

(2) close to the wound: early absolute hypoalgesia (up to 12–24 h postoperatively), increased by pre-emptive analgesia; modest relative/mechanical

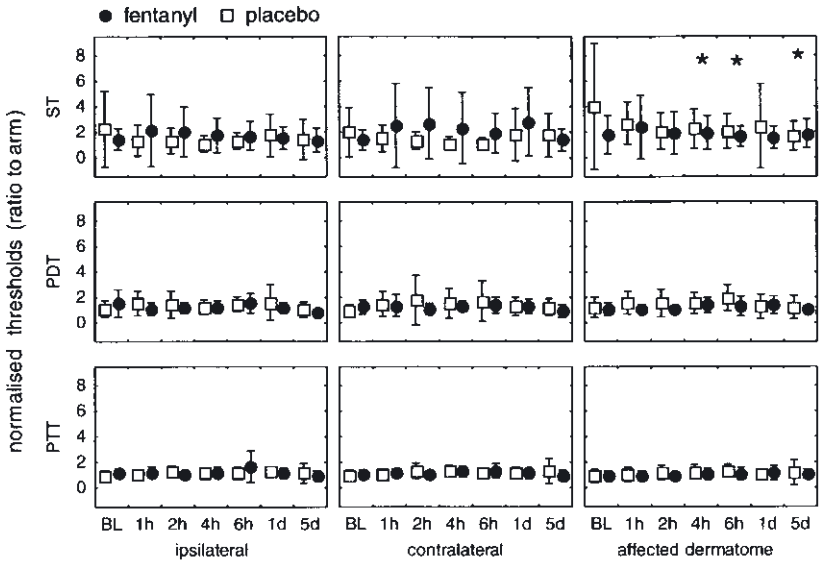

Fig. 4. Relative thresholds by electric skin stimulation (ratio; current threshold/arm threshold) (means, standard deviations) at preoperative baseline (*BL*) and 1, 2, 4, 6 and 24 h and 5 days after surgery for herniated intervertebral discs (after Wilder-Smith et al., 1996). Anaesthesia: isoflurane/nitrous oxide/oxygen ± 3 µg/kg fentanyl i.v. before intubation. Sites of measure: contralateral and ipsilateral to the back incision, and the dermatome of the nerve most affected by disc prolapse. Thresholds determined: sensation (*ST*), pain detection (*PDT*) and pain tolerance (*PTT*). Significant overall statistics (repeated measures ANOVA for drug, threshold site, threshold type and time): PTT > PDT > ST. For ST: placebo < fentanyl. Significances ($p < 0.05$) for specific times, sites and measures are marked on the graph: * = significant vs. BL, with values for placebo marked above and for fentanyl marked below the curves.

hyperalgesia (up to 5–7 d postoperatively) decreased or abolished by pre-emptive analgesia with opioid agonists or NMDA receptor antagonists, probably increased by preoperative sensory sensitisation (preoperative pain);

(3) on the wound: marked hyperalgesia (up to 4–5 d postoperatively), decreased but not abolished by analgesic pre-emption.

Thus psychophysical measures of sensory processing in the context of human surgery provide evidence that central nervous system neuroplastic change — both inhibitory and excitatory — takes place after surgical nociception and that this is positively influenced by relatively modest pre-emptive analgesic intervention. The presence of *inhibitory* central neuroplastic change is not one which would be predicted by or detectable in non-intact animal models of nociception, hence providing at least one partial explanation of the discrepancies between experimental animal and clinical human models of pre-emptive analgesia. In the studies cited, wound hyperalgesia tends to be more marked than secondary hyperalgesia and not completely abolished by pre-emptive analgesic intervention, suggesting that peripheral primary nociceptor sensitisation (see Reeh and Pethö, 2000, this volume) after nociception plays an important role in acute postoperative pain.

Altered sensory processing and clinical pain after surgery

Finally, we must turn to the question of whether there is a simple relationship between sensory change and clinical pain measures after surgical nociception. Of the selection of studies surveyed above, only one has demonstrated a formal correlation between

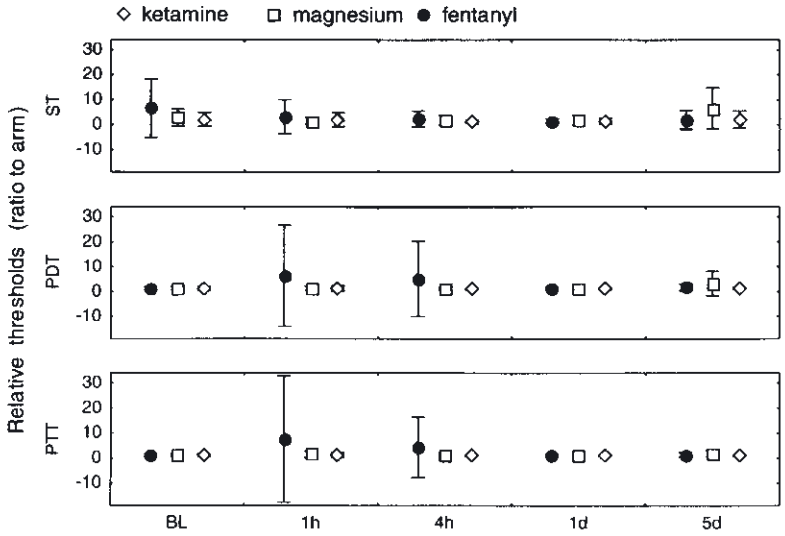

Fig. 5. Relative thresholds by electric skin stimulation (ratio: current threshold/arm threshold) (means, standard deviations) at preoperative baseline (*BL*) and 1, 4 and 24 h and 5 days after surgery for abdominal hysterectomy (after Wilder-Smith et al., 1998), measured close to site of surgical incision. Anaesthesia: isoflurane/nitrous oxide/oxygen supplemented by either fentanyl, magnesium or ketamine. Thresholds measured: sensation (*ST*), pain detection (*PDT*) and pain tolerance (*PTT*). Significant overall statistics (repeated measures ANOVA for drug, threshold site, threshold type and time): for fentanyl, thresholds overall 1–4 h > BL. There were no significant differences for specific times, sites and measures.

altered sensory processing and clinical pain measures. Moiniche et al. (1997), studying renal surgery patients, showed a modest correlation ($r = -0.4$) between secondary mechanical wound hyperalgesia and pain VAS at rest or on coughing. Some studies have found differences in primary (Tverskoy et al., 1994) or secondary wound hyperalgesia (Richmond et al., 1993; Stubhaug, 1997) due to analgesic pre-emption to be reflected by modest, mainly early and relatively short-lasting differences in pain intensity VAS or postoperative analgesia consumption. In our studies of back surgery and hysterectomy, the clear differences in sensory processing after surgery allied to differences in perioperative analgesic management were not reflected in differences in clinical pain measures such as pain VAS or morphine PCA consumption (Wilder-Smith et al., 1996, 1998). We have found no other studies establishing formal correlations between changes in sensory processing and clinical pain measures.

On present evidence we must conclude that while a link between altered sensory processing and clinical pain measures after surgery may well be present, it is likely to be weak. Such an outcome is to be expected on the basis of the multifactorial and multiaetiological nature of clinical pain, as explained above. Clearly, further investigations into the nature of the relationship between objective alterations in central sensory processing and subjective clinical pain measures are needed. This is even more the case for long-term pain and medical outcomes after surgery and their relation to alterations in sensory processing, as no studies of this type have been published so far.

Conclusions

The concept of pre-emptive analgesia purports that an analgesic intervention commenced before a nociceptive event will be more effective than the same

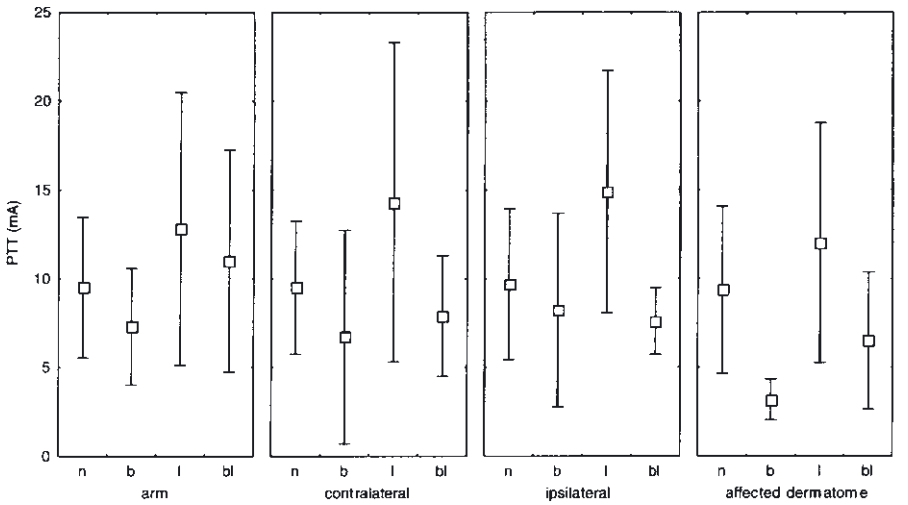

Fig. 6. Absolute thresholds by electric skin stimulation (means, standard deviations) preoperatively, before surgery for herniated intervertebral discs (after Wilder-Smith et al., 1999b). Sites of measure: arm, contralateral and ipsilateral to the planned back incision, and the dermatome of the nerve most affected by disc prolapse. Thresholds measured: sensation (ST), pain detection (PDT) and pain tolerance (*PTT*). Significant overall statistics (ANOVA for drug, threshold site, threshold type and pain presence): highly significant ($p < 0.000001$) effect of presence of moderate to severe pain (VAS > 5) (n = no pain; b = only pain in back; l = only pain radiating into leg; bl = both back and leg pain present) on thresholds. For PTT overall: l > n > b ($p < 0.05$).

analgesic intervention practised afterwards. Originally postulated on the basis of animal studies demonstrating central nervous system plasticity after nociception, this idea was introduced to clinical medicine with the hope of achieving substantial improvements in postoperative pain management. Unfortunately, such substantial improvements have not been forthcoming in the clinical context. In this chapter we have outlined why it has proven difficult to achieve the scale of improvement suggested to be possible by animal experimental models in the clinical arena. These difficulties involve obstacles to extrapolating from experimental models to the clinical situation, the challenges of achieving adequate clinical study designs, as well as problems and confusion regarding the choice of study endpoints relevant to pain outcomes in the clinical context.

Regarding pain endpoints for clinical studies, these need to be closer to the objective electrophysiological measures of altered central nervous system sensory processing used in animal studies of pre-emptive analgesia and neuroplasticity after nociception. We suggest that psychophysical testing, e.g. by sensory thresholds, provides such an objective measure suitable for clinical use. The altered central sensory processing reflected by psychophysical testing is much more likely to give a strong measure of neuroplasticity and pre-emptive analgesia than multifactorial and multi-aetiological subjective clinical pain measures such as pain intensity scales or postoperative analgesic use.

In summarising the data available on acute changes in central sensory processing after surgery to date we do in fact find clear evidence of acute neuroplastic change after surgery in humans (and animals). This neuroplasticity involves *both* inhibitory (e.g. descending inhibition) and excitatory (e.g. spinal sensitisation) components, whose net manifestation depends both on the time and place of measure. Pre-emptive analgesia with opioid agonists or NMDA receptor antagonists has a positive effect on both inhibitory (reinforcement) and excitatory (suppres-

sion) neuroplastic change after surgery. Evidence is further discussed that preoperative pain is also associated with altered central sensory processing, and thus perhaps with increased vulnerability to further post-nociceptive neuroplastic change, particularly in the absence of analgesia during surgical nociception.

At present these neuroplastic changes in central nervous system sensory processing have been demonstrated acutely, i.e. for up to 7 days postoperatively. There appears to be a weak relationship between changes in psychophysical measures and clinical subjective pain measures (pain VAS, analgesia use), but any such correlations are little and poorly defined at present. No studies have investigated the relationship between psychophysical measures of neuroplasticity and longer-term, chronic pain or medical outcomes after surgery to date. More studies are needed to better define the relationship between surgical nociception, neuroplastic change in central nervous system sensory processing, subjective clinical pain measures, and long-term chronic pain and medical outcomes of surgery.

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18. *Article* - Anaesthesia, Analgesia and Surgery: Neuroplasticity and Pain

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Changes in Sensory Processing After Surgical Nociception

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Nociception results in peripheral and central changes in sensory processing. These changes are considered to significantly contribute to postoperative pain and its outcome. Objective measures of changes in sensory processing are now being studied in humans after surgery. Surgical nociception leads to both central excitation (eg, spinal sensitization) and central inhibition (eg, descending inhibition), with inhibition being the dominant response during the first day or so after surgery. Analgesia commenced before surgery (preemptive analgesia) depresses central sensitization and enhances central inhibition. Patients operated on under nonanalgesic anesthesia may exhibit rebound central sensitization for up to 5 days postoperatively after the cessation of postoperative opioid analgesia. There is only a weak relationship between the described objective changes in sensory processing after surgical nociception and subjective clinical pain measures such as pain intensity scales or post-operative analgesic consumption.

The concept that nociceptive input to the central nervous system alters subsequent sensory processing became current in the 1980s. Experimental evidence was published demonstrating that afferent nociceptive signals of sufficient intensity alter the behavior of spinal dorsal horn neurons [1–3]. Subsequently, such alterations in sensory processing were also shown to be present more centrally, *eg*, in the thalamus [4,5]. From the introduction of this concept, such alterations in sensory processing have been considered to play a significant role in explaining the clinical symptomatology of pain after surgery, and thus to offer a key to improving the clinical management and outcome of postoperative pain [6,7].

Most of the early studies of nociception and central sensory change involve nonintact (*ie*, decerebrate or spinalized) animals and demonstrate excitation of dorsal horn neuronal function [1–3]. Excitation is most easily elicited by C-fiber inputs, which are most effective if repeated, thus leading to signal summation, temporal as well as spatial [8–10]. For afferent nociceptive input from noninflamed tissues, temporal summation predominates, whereas spatial summation plays the major role in inflamed tissues. Such summated input leads to long-lasting reductions in dorsal horn neuron membrane potentials (*eg*, long-term potentiation [11]) and thus to long-lasting depolarization and discharge. These changes outlasting the original afferent nociceptive input can persist up to minutes and may even become autonomous, resulting in spontaneous discharge, a phenomenon termed "wind-up." The consequences of the described alterations in dorsal horn neuronal function are:

- reduction of the neuronal firing threshold;
- increase in the neuronal response associated with a given stimulus;
- after-discharging or spontaneous neuronal signaling;
- spread of increased sensitivity to adjacent neurons.

The Biochemical Basis of Altered Central Sensory Processing

The changes in dorsal horn neuronal function are moderated by excitatory amino acid (*eg*, glutamate, aspartate) and neuropeptide (*eg*, substance P, neurokinin A) release from the primary nociceptive afferents into the synaptic cleft. Antagonists to the *N*-methyl-D-aspartate (NMDA) receptor (for the excitatory amino acids) or the tachykinin receptor (for the neuropeptides) will block both the electrophysiologic and behavioral consequences of nociceptive input to the dorsal horn [12]. NMDA-receptor activation is obligatory to achieve central sensitization, and is dependent on the release of soluble GMP cyclase and the continuing production of nitric oxide [1,13]. The binding of excitatory amino acids (or neuropeptides) to dorsal horn neuron receptors is followed by the slow synaptic dorsal horn potentials and thus the electrophysiologic changes described previously. It is accompanied by increased calcium entry via calcium ionophores due to ligand-gated (NMDA or tachykinin receptor activation) or voltage-gated (membrane depolarization) mechanisms [7]. The rise in intracellular calcium levels results in increased second messenger (*eg*, cyclic GMP) and protein kinase C activity. This leads to positive feedback to the NMDA receptors and the expression of early intermediate genes (*eg*, *c-fos*, *B-jun*) involved in the production of substances regulating sensory sensitivity (*eg*, dynorphin, which produces hyperalgesia) [7].

Central Neuroplasticity

The phenomenon of altered central sensory processing described so far is termed central neuroplasticity or sensitization and manifests itself by:

- hyperalgesia (more pain felt for a given stimulus);
- allodynia (a previously nonpainful stimulus becomes painful);
- windup (prolonged or spontaneous pain);
- secondary hyperalgesia (areas beyond the injured tissue become hypersensitive).

Central neuroplasticity (secondary hyperalgesia) after nociception needs to be distinguished from peripheral sensitization processes (primary hyperalgesia) resulting from chemical sensitization of tissue nociceptors by the many biochemical substances (the "inflammatory soup") released by the tissue damage caused by nociception [14]. It should be emphasized that central sensitization is not only due to dorsal horn neuronal sensitization and thus input facilitation, but also due to loss of inhibitory inputs to the same cells [7].

Sensory Change and the Concept of Preemptive Analgesia

Of interest was the discovery that it is easier to prevent dorsal horn sensitization due to nociception (*eg*, by giving morphine before the nociceptive stimulus) than to suppress sensitization after it has been induced [15,16]. This discovery gave rise to the hypothesis of preemptive analgesia, which postulates not only that an analgesic intervention performed before a nociceptive event will be more effective than one performed afterwards, but also that the effects of such an intervention will significantly outlast the pharmacologic duration of action of the analgesic used [17]. The idea of preemptive analgesia not only suggested an attractive therapeutic approach to the management of postoperative pain, it also provided a first means of testing and understanding the clinical relevance of the concept of changes in sensory processing due to nociception.

In the last decade, a large number of studies have been performed to test the concept of preemptive analgesia. The initial series of such studies, performed in the first half of the 1990s, showed disappointing results, with either absent effects or clinically modest and short-lasting reductions in analgesic consumption or subjective pain measures after surgery. A number of editorials and reviews of this topic published at the time suggested the need for improved study designs in order to obtain more convincing results [18–21]. Many preemptive analgesia studies have been carried out since that time, incorporating the design improvements suggested (*eg*, effect proven [22–31]; no effect proven [32–37]). Although this has resulted in more success in proving an effect of preemptive analgesia for certain substances (notably opioids, local anesthetics, and NMDA-receptor antagonists), the effects demonstrated have remained clinically modest and of short duration. Thus the first test of the relevance of altered post-nociceptive sensory processing to clinical pain resulted in a notable discrepancy between the significant findings expected from animal studies and the clinically modest effects actually demonstrated in human studies.

The Problems of Preemptive Analgesia in Clinical Practice

Why is this? In the extrapolation under consideration from basic animal to human clinical models, three major changes occur:

- a change from minor, short-lasting, usually monomodal nociception to major, long-lasting, usually multimodal nociception;
- a change from a nonintact animal model (*ie*, spinalized or decerebrate) to an intact human model;
- a change from objective measures of sensory processing (*ie*, electrophysiologic or psychophysical) to subjective pain measures (*ie*, pain ratings or analgesic consumption).

Whereas the first change is of a more quantitative character, and thus more easily dealt with by design adaptations (this is particularly the case in the later preemptive analgesia studies), the other two changes are of a more fundamental and qualitative character. Nociception impinging on the central nervous system can be expected to have fundamentally different results for intact as compared with nonintact organisms, both with regard to the changes resulting and with regard to the defending mechanisms initiated secondarily. Thus a spinalized animal model will neither deliver information on thalamic sensitization nor inform about descending inhibitory controls to the dorsal horn. Equally, it must be realized that objective measures of sensory processing and subjective ratings of pain measure are quite different things, and that they are not necessarily well related.

The human experience of pain is a subjective one, affected by much more than just alterations of neuronal processing at various levels of the central nervous system. The pain experience is much influenced by factors quite unrelated to the original nociceptive event. This multifaceted nature of the human subjective pain experience is correctly reflected in the IASP definition of pain [38]. Objective psychophysical or electrophysiological measures of altered sensory processing will therefore always provide different types of information than subjective, clinical measures of the total pain experience, such as pain scores, pain relief, or analgesic consumption. It should also be noted that even within the area of subjective pain measurement, the relationship between individual subjective pain measures is complex: *eg*, no simple, consistent linear relationship between pain relief and analgesic consumption has been established in the postoperative context [39].

From Experimental to Clinical Measures of Pain

In short, the net effect of nociception on the intact central nervous system is complex, and subjective, clinical pain measures cannot be assumed to correlate closely with lower-order (*ie*, spinal, brain stem, midbrain) changes in sensory processing as measured by psychophysical or electrophysiologic methods. It is thus unrealistic to expect to extrapolate from simple nonintact animal models of monomodal nociception involving electrophysiologic measures to the complex situation of multimodal clinical nociception in intact human patients and their subjective pain experience. The objective sensory changes resulting from surgical (or other) nociception therefore have to be studied directly—not assumed or extrapolated—if we are to understand the effects of nociception, and what effects its modulation will provide. Indeed, direct quantification of the lower-order objective changes in sensory processing due to nociception will provide another advantage: as these changes are much closer to the nociceptive input than subjective pain measures, they will provide a better reflection of the amount of nociception and damage the body has been subjected to. Thus objective measures of the alterations in sensory processing due to nociception should supply much better predictive parameters for ultimate pain (and disease) outcomes of the patient—the ultimate and satisfying therapeutic goal of all nociceptive modulation. In a second step, the relationship between lower-order objectively quantified changes in sensory processing after nociception and subjective pain measures then needs to be determined.

Objective Clinical Measures of Sensory Change Due to Nociception

Psychophysical measures such as cutaneous sensation or pain thresholds are relatively easy to apply to the clinical context, not too time-consuming, and well validated, on the condition that subject and tester are adequately trained [40]. Ideally, such thresholds should be measured at multiple sites to obtain a comprehensive picture of sensory change. The measures should comprise at least the following sites:

- on the wound to include primary hyperalgesia;
- close to the wound (approximately 10 to 15 cm) to cover secondary hyperalgesia;
- distant from the wound to include generalized effects such as descending inhibition.

Other sites may be included to cover areas of referred pain from internal organs or of convergent innervation. Measuring multiple sensory modalities (sensation, pain detection, pain tolerance) or using multiple stimulating modalities (mechanical, electric, thermal, or dermatomal vs neuronal) provides further comprehension of the alterations in sensory processing resulting from nociception.

Defining the Changes in Sensory Processing Due to Nociception in Humans

Since the early 1990s, a number of clinical human studies have been performed to identify the changes in central sensory processing due to surgical nociception. Most of these studies have involved psychophysical measures, mostly using either electrical or mechanical stimulation. A few studies involved electrophysiologic tests, either somatosensory-evoked potentials or the nociceptive flexion reflex (R-III reflex) [41,42]. Due to the onerous nature of such investigations, these studies involved single postoperative measures in small patient collectives.

Electrical thresholds

We have found five studies in the literature to date investigating changes in electrical cutaneous thresholds after surgery [40–42,43•44•]. The results of these studies are summarized in Table 1. In the first study of its kind, Lund *et al.* [41] found electrical sensation thresholds distant to infraumbilical hysterectomy incision to be increased 48 hours postoperatively, with accompanying reductions in the P1, N1, and P2 somatosensory-evoked potential peak amplitudes. In a second study from this institution [42], pain tolerance thresholds to direct sural nerve stimulation (convergent innervation with the gynecologic laparotomies performed) were decreased 48 to 96 hours post surgery, whereas the nociceptive flexion reflex responses showed trends toward increased amplitude and decreased threshold. Taken together, these results point toward generalized central sensory inhibition distant to surgery and central (spinal) sensory excitation in the innervation areas involved by surgical intervention.

These first conclusions were strengthened and expanded in a study of patients undergoing surgery for herniated intervertebral discs, of which half had nonanalgesic general anesthesia (isoflurane and placebo) and half had the same general anesthesia supplemented by fentanyl [40]. All patients received patient-controlled morphine analgesia for the first 24 postoperative hours. The authors found that sensory (*ie*, nonnociceptive) as well as pain detection and tolerance (*ie*, nociceptive) electrical thresholds near to and distant from the wound were increased during the first 4 to 6 hours postoperatively, returning to preoperative baseline values by 24 hours after surgery (Fig. 1). The fact that nonnociceptive thresholds (not affected by opioids [45]) were also involved suggests that these changes were not due to the morphine analgesia. The hyposensitivity and hypoalgesia were more pronounced nearer to the wound and in those patients with analgesic anesthesia. At 5 days postoperatively, pain thresholds in patients with nonanalgesic anesthesia were reduced compared to preoperatively. Such hyperalgesia suggests the presence of central sensitization. This sensitization was probably suppressed by the morphine analgesia during the first 24 hours, pointing to the much greater impact of intraoperative analgesia (*ie*, preemptive analgesia) as compared with postoperative analgesia.

Table 1. Summary of Changes in Sensory Processing After Surgery in Humans

Thresholds to cutaneous dermatomal electrical stimulation
On wound (primary hyperalgesia)
Not studied
Near wound (secondary hyperalgesia)
Hyposensitivity and hypoalgesia; present for first 24 hours postoperatively
Inhibition increased by preemptive analgesia (opioids, ketamine, magnesium)
Hypersensitivity and hyperalgesia masked but demonstrable (relative thresholds)
Excitation depressed or prevented by preemptive analgesia
Without preemptive analgesia, hyperalgesia may become visible after stopping opioid analgesia up to 5 days postoperatively
Distant to wound (generalized effects)
Hyposensitivity and hypoalgesia; present for first 24 hours postoperatively, less than near wound
Increased by preemptive analgesia (opioids, ketamine, magnesium)
Decreased cortical somatosensory-evoked potential amplitudes
Conclusions
Central descending inhibition is dominant for first 24 to 48 hours
Central (spinal) excitation is initially masked, but demonstrable
Central sensitization is suppressed by preemptive analgesia
In absence of preemptive analgesia, central sensitization may become overt up to 5 days postoperatively
Thresholds to direct transcutaneous electrical nerve stimulation
In convergent innervation area
Hyperalgesia 48 to 96 hours postoperatively
Increased R-III reflex, decreased R-III threshold
Conclusions
Spinal excitation or sensitization present at 48 to 96 hours postoperatively
Thresholds to cutaneous mechanical stimulation
On wound (primary hyperalgesia)
Intense hyperalgesia for 4 to 5 days, generally gone by 8 days postoperatively
Decreased by preemptive analgesia (fentanyl, ketamine)
Near wound (secondary hyperalgesia)
Less intense hyperalgesia than on wound for 4 to 5 days, generally gone by 8 days postoperatively
Area of hyperalgesia reduced by preemptive analgesia (ketamine) for up to 1 week postoperatively
Distant to wound (generalized effects)
Thresholds generally unchanged during first postoperative week
Conclusions
Mechanical thresholds less sensitive to descending inhibition
Wound (primary) hyperalgesia partially sensitive to preemptive analgesia
Clear signs of central sensitization for 4 to 5 days postoperatively
Central sensitization depressed by preemptive analgesia

R-III—nociceptive flexion reflex.

The presence of sensitization in the group with nonanalgesic anesthesia is supported by the fact that the relative nonnociceptive (sensation) thresholds (*ie*, normalized by means of division by the threshold at the site distant to surgery in order to eliminate generalized inhibitory effects) were decreased up to 5 days postoperatively (Fig. 2). These results confirm the presence of central sensitization as a result of surgical nociception, but which can be prevented by analgesic anesthesia for up to 5 days postoperatively. It should be noted that the body's dominant response to surgical nociception in the early postoperative period is generalized sensory inhibition, enhanced by intraoperative analgesic anesthesia and at least partially independent of postoperative morphine analgesia. In the presence of adequate analgesic management (*ie*, analgesic supplementation of anesthesia, postoperative analgesia by patient controlled analgesia), changes in sensory processing due to surgical nociception seem to be relatively short lived, returning to normal by 5 days postoperatively.

Further studies of electrical cutaneous thresholds in patients who have had a hysterectomy confirm and elaborate these results. One such study [43•] compared analgesic supplementation throughout general anesthesia by opioid receptor agonists (fentanyl) and NMDA-receptor antagonists (ketamine and magnesium), confirming that thresholds near to and distant from the site of surgery are increased during the first 24 hours after surgery, returning to baseline values at 5 days (Fig. 3). There was no sign of sensitization in any of these patients, either in absolute or relative thresholds, suggesting that the three substances provided equally effective intraoperative antinociceptive prophylaxis. Another study providing less analgesic supplementation during abdominal hysterectomy also confirmed increases in postoperative absolute pain tolerance thresholds distant to the surgery [44•]. However, pain thresholds did not increase significantly near to the incision, suggesting more central sensitization than in the previous study due to less analgesic

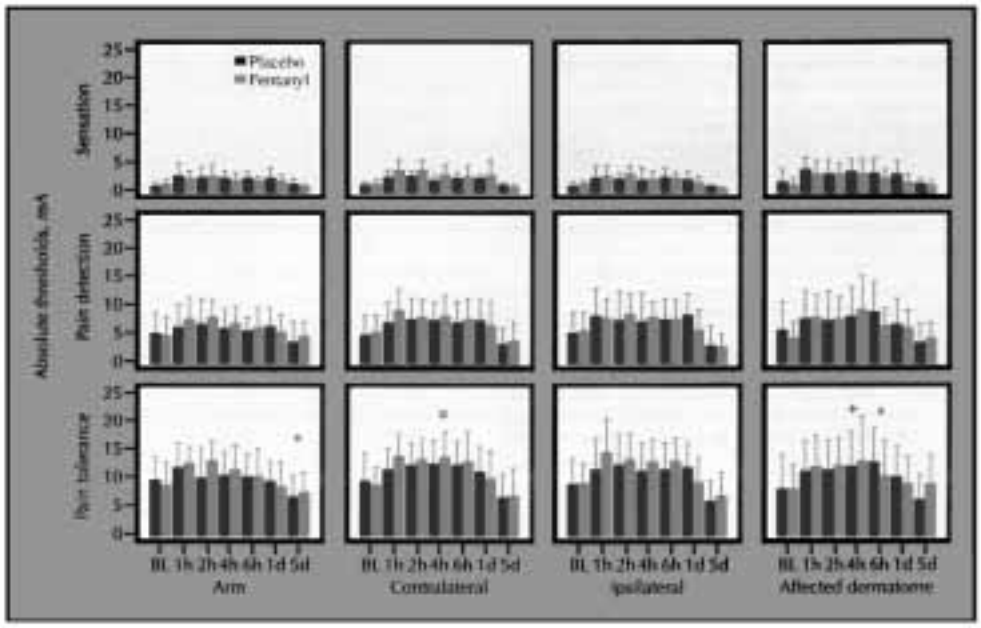

Figure 1. Absolute electric skin thresholds (mA, means, SD) at preoperative baseline (BL) and 1, 2, 4, 6, 24 hours and 5 days after herniated intervertebral disc surgery (after [40]). Statistics—significant ($P < 0.05$) overall differences (repeated measures ANOVA for drug, threshold site, threshold type, and time): fentanyl greater than placebo; PTT > PDT > ST; arm < contralateral = ipsilateral = affected dermatome; 4 hours > BL. * = significant versus BL for placebo group; x = significant versus BL for fentanyl group; + = significant versus BL for both groups. ANOVA—analysis of variance; PDT pain detection; PTT—pain tolerance; ST—sensation.

supplementation. This interpretation is supported by the observation that pain thresholds distant to surgery were decreased compared with the preoperative baseline at 4 days after surgery. Again, this would suggest the reappearance of sensitization after the cessation of postoperative opioid analgesia. Interestingly, pain thresholds increased more during morphine infusion than tramadol infusion for postoperative analgesia. This study also studied rectal distension thresholds, which increased in the immediate postoperative period and then returned to baseline. These results would suggest moderate somatic but no visceral sensitization with lower intraoperative analgesic supplementation than in the study comparing fentanyl, ketamine, and magnesium supplementation [43•].

Mechanical thresholds

To date, four studies have formally investigated changes in mechanical sensory processing after surgery [46–48,49•]. The results are also summarized in Table 1. Richmond *et al.* [46] provided only postoperative relative sensation and pain detection thresholds close to the incision for abdominal hysterectomy, calculated relative to the forearm. At 24 and 48 hours postoperatively, these values were negative in patients receiving nonanalgesic general anesthesia and positive in those with analgesic supplementation (morphine), suggesting the presence of central sensitization inhibited by analgesic supplementation of anesthesia. A study of pain detection thresholds immediately on the hysterectomy wound provided only postoperative values, with wound hyperalgesia being less with analgesic supplementation of anesthesia by fentanyl or ketamine than without [47]. In another study of hysterectomies, Moiniche *et al.* [48] demonstrated the presence of intense hyperalgesia directly on the wound compared with preoperative values for up to 4 days post surgery, with a return to baseline values only at 8 days. Close to the wound, less intense mechanical hyperalgesia was found with a similar time course as for primary hyperalgesia, whereas distant to the wound, mechanical pain detection thresholds were unchanged throughout the 8-day observation period of the study. Stubhaug [49•], investigating patients after open renal surgery, showed that the area of hyperalgesia surrounding the wound was decreased by ketamine supplementation of general anesthesia for up to a week after surgery. These studies confirm the presence of central sensitization after surgical nociception, though suggesting that mechanical threshold measurement is less sensitive to central inhibition.

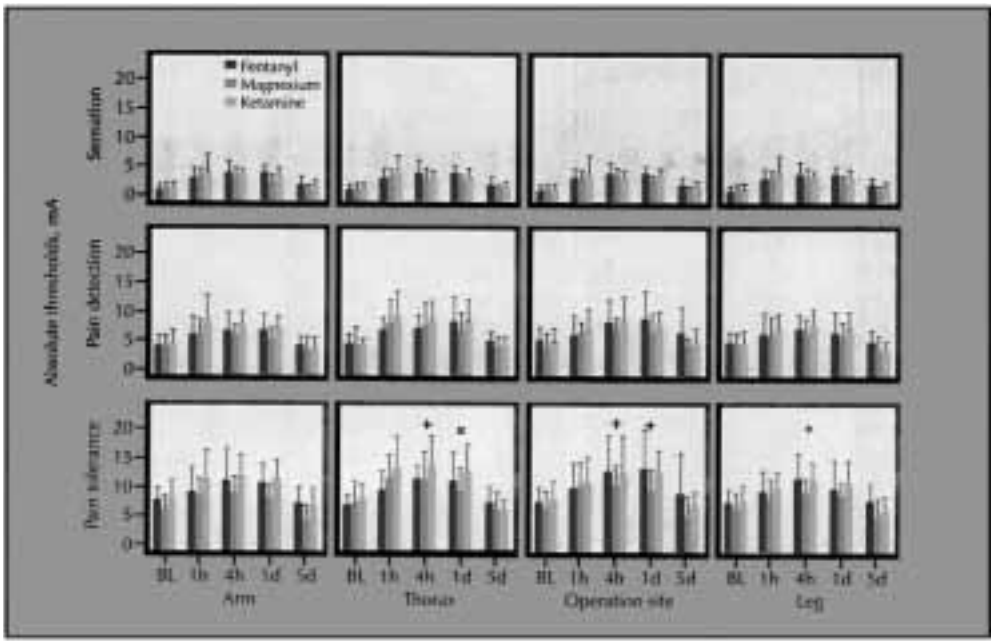

Figure 2. Relative electric skin thresholds (ratio = current threshold divided by arm threshold, means, SD) at preoperative baseline (BL) and 1, 2, 4, 6, 24 hours and 5 days after herniated intervertebral disc surgery (after [40]). Statistics—significant ($P < 0.05$) overall differences (repeated measures ANOVA for drug, threshold site, threshold type, and time): PTT > PDT > ST. For ST: placebo < fentanyl.
* = significant versus BL for placebo group. ANOVA -analysis of variance; PDT—pain detection; PTT—pain tolerance; ST—sensation.

Relationships Between Objective and Subjective Pain Measures

To complete this discussion, we briefly address the question of the relationship between the sensory changes after nociception described previously and subjective clinical pain measures. Only one of the studies mentioned earlier has provided an explicit correlation between changes in sensory processing and clinical pain measures [48]. Moiniche *et al.* [48] calculated a modest correlation ($r = -0.4$) between pain visual analogue scale (VAS) at rest or on coughing and secondary hyperalgesia (close to the wound). Other studies have found clear differences in objective measures of sensory processing due to preemptive analgesia without finding any differences in subjective clinical pain measures such as pain intensity VAS or morphine consumption [40,43•]. A third category of studies has found significant differences in primary or secondary wound hyperalgesia to be reflected by minor differences in pain VAS or analgesic consumption, mainly evident early and of relatively short duration [46,47,49•]. These findings are compatible with the presence of a weak link between changes in sensory processing after nociception and clinical pain measures. Such a weak relationship fits well with the multiple origins of and factors involved in the clinical pain experience, as discussed previously. Further research is obviously needed to better elucidate the relationships between objective and subjective pain measures, as well as the relationship of both these classes of measures to long-term pain and clinical outcomes.

Conclusions

At present we only have acute data (*ie*, for about 1 week) on changes in central sensory processing due to surgical nociception in humans. There is convincing evidence of central neuroplasticity after surgery, both inhibitory (*eg*, descending inhibition) and excitatory (*eg*, spinal sensitization). Under normal circumstances, these changes appear to return to baseline within about a week. Central neuroplasticity is positively influenced by preemptive analgesia, with depression of excitation and enhancement of inhibition by both opioid agonists and NMDA-receptor antagonists. At best, there is a weak relationship between central changes in sensory processing and the subjective, clinical manifestations of nociception, such as pain intensity VAS or postoperative analgesia consumption. We therefore suggest that future studies of surgical nociception and its modulation should include objective measures of changes in central processing in order to achieve better understanding of etiologic and therapeutic mechanisms.

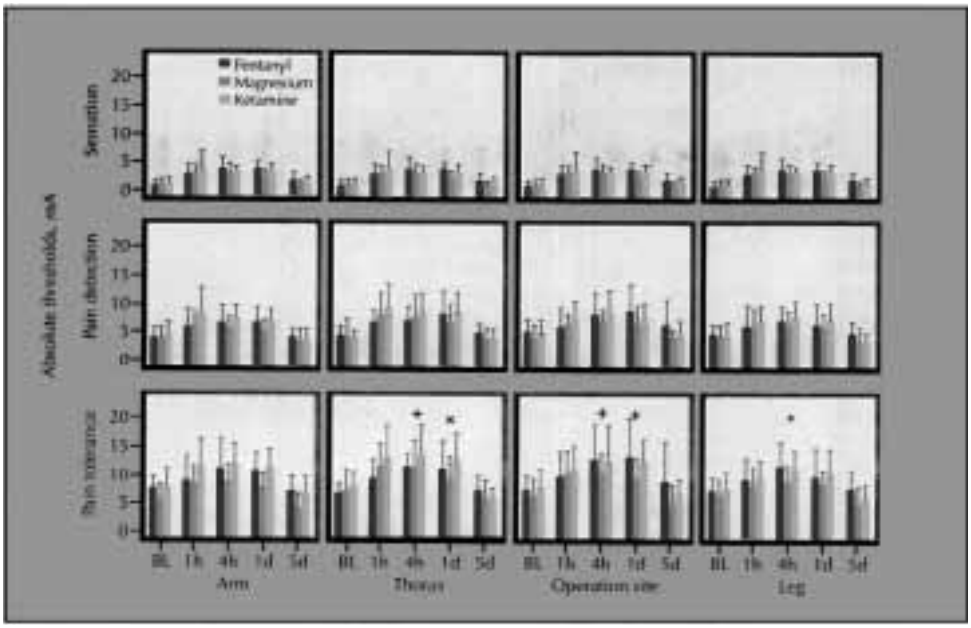

Figure 3. Absolute electric skin thresholds (mA, means, SD) at preoperative baseline (BL) and 1, 4, 24 hours and 5 days after abdominal hysterectomy (after [40]). Statistics—significant ($P < 0.05$) overall differences (repeated measures ANOVA for drug, threshold site, threshold type, and time): PTT > PDT > ST; 1 to 24 hours > BL. * = significant versus BL for fentanyl group; x = significant versus BL for ketamine group; + = significant versus BL for both groups. ANOVA—analysis of variance; PDT—pain detection; PTT—pain tolerance; ST—sensation.

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- • Of special interest
- •• Of outstanding interest

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VI

DISCUSSION, IMPLICATIONS AND OUTLOOK

19. QUANTITATIVE SENSORY TESTING AND NEUROPLASTICITY: IMPLICATIONS FOR SURGICAL PAIN MANAGEMENT

The research presented here permits, we would suggest, the drawing of a number of conclusions relevant to surgical pain and nociception and its medical management. The first set of conclusions pertains to things which can now be considered reasonably well-proven and which could thus be applied to medical practice now, while the second set concerns future development and research in this area. It must be emphasised in this context that quantitative sensory testing (QST) monitoring of surgical nociceptive neuroplasticity for nociception management is at an early stage. Considerable development and research are necessary to fully understand and validate this area and it practical implications, but it would appear that its application carries the promise of introducing a new level of understanding to the management of surgical nociception. In this final chapter we will attempt to provide a brief overview of the implications of our investigations, both present and future.

19.1. Immediate Implications for Clinical Practice

19.1.1. Feasibility of QST Use in the Clinical Context

The body of research introduced here reports a large number of QST measures in routine patients in the clinical setting. Electrical threshold determinations in this context were well-accepted, and proved relatively simple and rapid regarding both instruction and actual measures. The equipment (nerve stimulator, self-adhesive ECG electrodes) is simple and affordable. At present, thermal (Peltier thermode) thresholds are less practicable, being more onerous to obtain. Although the widespread introduction of routine clinical QST awaits development of the equipment used, we would consider that, with appropriate training and organisation, electrical stimulation techniques can be directly introduced into clinical practice now for selected patients.

19.1.2. Effectiveness of QST for Demonstrating Analgesia and Surgical Neuroplasticity

In all of the investigations presented here, it proved possible to show, follow and differentiate the changes in sensory processing (i.e. neuroplasticity) accompanying analgesia and surgical nociception. Thus the QST methods presented are an effective means of making surgical neuroplasticity visible in the clinical context. QST offers the prospect of a useful new endpoint for the management of surgical pain and nociception, with a real potential for providing novel, objective information. Such knowledge about surgical neuroplastic change - and thereby about underlying mechanisms of nociception -is both relevant to clinical management and not obtainable by established clinical methods.

19.1.3. QST vs. Clinical Pain Measures in Surgical Pain and Nociception Management

The neuroplasticity demonstrated to accompany surgery in our studies is generally only weakly and indirectly reflected in clinical pain measures such as pain scores or analgesia use. This is not surprising in view of the of the complexity of subjective pain experience, with its multifactorial nature, mechanisms and aetiologies (1,2) and involving many factors quite unrelated to the original nociceptive stimulus. The investigations under discussion here clearly show that clinical pain measures are not a reliable or complete indicator of underlying changes in central nervous system sensory processing, and thus of the mechanisms involved in the production of surgical pain. Clinical pain measures and QST results must therefore be regarded as providing different but complementary kinds of information useful in the management of surgical pain and nociception.

19.1.4. Nature of the Surgical Neuroplasticity Demonstrated by QST

Our results illustrate the complexity of the neuroplastic response to surgical nociception. We have shown and detailed the complexity to comprise a number of aspects, including mechanisms (e.g. excitatory vs. inhibitory), structures involved (e.g. spinal vs. supraspinal) and time course (e.g. acute vs. subacute). If we are to properly understand surgical neuroplasticity in a specific patient or situation, it is clearly important for all these aspects to be taken into account and made visible by the QST methods employed. We would suggest that the QST design features presented in our studies, particularly regarding stimulus characteristics, topographical and temporal aspects, represent the minimum necessary to achieve an acceptable understanding of the complex neuroplastic response to surgical nociception. The question of the desirability and practicability of including multiple stimulus modalities (e.g. thermal, mechanical, electrical) awaits future studies.

19.1.5. Towards more Effective Surgical Pain Management

QST is the basis for the necessary shift to mechanism-based surgical pain management by providing useful insight into the mechanisms associated with surgical nociception and its management in a number of ways. Firstly, it provides a way of differentiating nociceptive alterations in the function of - and the balance between - different parts of the central nervous system (e.g. spinal vs. supraspinal, excitation vs. inhibition) in a way which global clinical pain measures never can. Secondly, by allowing quantification of changes in lower-order (i.e. more caudal) sensory processing, it takes us much closer to the nociceptive load the body experiences, and thus potentially to metabolic, immunological or trophic consequences for the body as a whole. Finally, QST in our studies is sensitive to modulation of the neuroplastic response to nociception by both intrinsic and extrinsic factors. Thus it is possible to make visible the mechanisms by which such factors (e.g. various analgesic drugs) affect surgical pain and nociception. Attention must be called here to the hitherto largely neglected but important role which intrinsic inhibitory

mechanisms play in the neuroplastic response to surgical nociception, pointing to the need to include management of intrinsic inhibitory responses in future therapeutic analgesic strategies. Thus, use of QST-demonstrated nociceptive neuroplasticity brings with it not only the potential for understanding the mechanisms underlying the pain of surgery, but also of providing a defined, more objective, mechanism-based endpoint for the rational choice and control of existing - and new - drug or other measures in surgical nociception management. Immediate practical consequences for such management would include starting effective (e.g. opioid or NMDA-receptor-based) analgesia before surgery and to continue with it into the postoperative period, as well as the need to take into account endogenous antinociceptive inhibitory responses in the planning of perioperative analgesia (e.g. the effects of preoperative pain or ketorolac therapy).

19.2. Future Implications for Development and Research

19.2.1. Development: Integrating QST into Routine Clinical Management of Surgical Nociception

In order to maximise benefit from the advantages of mechanism-based as opposed to symptom-based management of surgical nociception, an effort will be needed to ensure its broader introduction into routine clinical practice. In this context, two measure will be of importance: Firstly, the practicability of using QST in the clinical context will have to be increased via further development and validation of testing paradigms and the equipment used. In this context automation of both testing and data collection via appropriate application of computer technology will play an important role. Secondly, systematic research will have to be undertaken to identify the patient subgroups most likely to benefit from QST/mechanism-based management of surgical nociception, both as a group and as individual patients. This would involve identification of patients/groups especially vulnerable to undesirable surgical neuroplasticity and pain outcomes, and those particularly likely to benefit from targeted, mechanism- and QST-based nociception management strategies.

19.2.2. Research: QST, Mechanism-based Nociception Management and Disease Outcomes Modification

Nociceptive neuroplasticity is also considered to be the basis for - and an integral part of - the chronification process leading to the progression of acute pain to various chronic pain syndromes (3-5). In this context, the application of QST and mechanism-based pain management may prove useful both in identifying the mechanisms involved in chronification, and in conceiving strategies for preventing or modulating the chronification process. The neuroplastic changes having been shown to take place after surgery are of the type considered to be involved in pain chronification mechanisms (3,4,6,7). Therefore the demonstration that certain types of pre-emptive analgesia can inhibit such changes in sensory processing represents a first step in the elucidation of promising strategies for preventing pain chronification. There is clearly a need for studies investigating the course of neuroplastic changes after surgical (or other) nociception, as well as the effect of putative mechanism-based preventive management strategies, over a much

longer time-frame than at present available. Furthermore, as discussed above, nociceptive neuroplasticity is likely to be much closer to original nociceptive load and hence outcome-relevant metabolic, immunological and trophic effects. Thus future studies in this field will also have to investigate the relevance of QST-derived neuroplasticity to long-term outcomes of surgery, and the possibilities of modulating these via appropriate nociceptive management.

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VII

SHORT SUMMARIES

SHORT ENGLISH SUMMARY

Nociception, including that caused by surgery, is associated with changes in peripheral and central nervous system processing. This neuroplasticity is considered an important mechanism for pain after surgery, both acute and chronic. However, despite greatly increased theoretical understanding from animal work linking nociceptive biomolecular mechanisms and neuroplasticity, the clinical management of surgical pain continues to represent a major practical challenge. Because adequate pain management has the potential to reduce postoperative morbidity and improve surgical outcomes, this challenge clearly warrants action.

It would appear logical that therapeutic management of surgical pain is most successful if based on an understanding and knowledge of the mechanisms acting during surgical nociception. However, at present virtually all therapeutic management of surgical pain and nociception is based upon subjective clinical pain symptomatology and measures. There is thus a clear need for the development of defined, more objective, clinically useful measures upon which to base the shift from symptom-orientated to mechanism-based pain management. The aim of this work is to provide the basis for such a shift by validating nociceptive neuroplasticity as an objective and feasible endpoint for surgical nociception and its therapy.

We have addressed this aim in a number of ways. After the introductory user's guide in Section I, Section II provides a theoretical background to our subsequent research. We provide animal data linking nociception, biomolecular mechanisms and neuroplasticity (chapter 2), discuss the practical aspect of the measure of nociceptive neuroplasticity by quantitative sensory testing (QST) as well as its relationship to pain (chapter 3), and introduce a detailed plan and rationale for the research to be presented (chapter 4).

In the subsequent two sections (Sections III-IV), we portray the results and application of our research using QST for quantifying analgesia and surgical neuroplasticity. First, in Section III, we validate QST for monitoring altered sensory processing in the simpler context of investigating analgesia. Here we present studies demonstrating the antinociceptive properties of both intravenous anaesthetics (chapter 6) and opioid analgesics (chapter 7) by QST using thermal or electrical stimulation. Subsequently, in Section IV, we report the results of our systematic investigation of surgical nociceptive neuroplasticity using QST (chapters 10-15). On the basis of these studies involving over 200 patients we demonstrate the feasibility of using QST in the clinical context. Furthermore, we show that the use of the objective endpoints of nociceptive neuroplasticity provides novel information which is clinically useful and not obtainable by other means such as subjective pain measures (summary in chapter 16). In particular we show that surgical nociception is followed by a complex neuroplastic response which varies over time, and which involves both excitation and inhibition of spinal and supraspinal origin. Interestingly, preoperative pain is also associated with neuroplasticity, and the

inhibitory neuroplasticity accompanying acute preoperative sciatica is seen to reduce postoperative excitatory neuroplasticity for up to 5 days. Perioperative analgesia generally exerts a positive effect in reducing excitatory postoperative neuroplasticity, although the details of these effects vary according to drug, mode of application and time. Postoperative neuroplasticity is only weakly and incompletely reflected by clinical pain measures such as pain scores or analgesia use.

The last two sections (Sections V-VI) discuss practical applications and implications of QST and nociceptive neuroplasticity for surgical pain and nociception management. Section V includes two review articles discussing the impact of the concept of nociceptive neuroplasticity on the long-standing pre-emptive analgesia debate (chapter 17) and practical aspects of QST use in the surgical context (chapter 18). In summing up, chapter 19 addresses the question of the applicability and impact of QST and nociceptive neuroplasticity on the present and future practice of perioperative pain management. QST can feasibly be introduced into clinical practice *now* as a means of objectively monitoring nociceptive neuroplasticity, thus commencing the transfer from symptom-orientated to mechanism-based pain management. In future, much more use will have to be made - both in research and clinical practice - of its unique potential to provide information not obtainable by classic measures of the subjective pain experience. Here, a particularly promising application will be the concept of nociceptive load modulation to alter long-term pain and medical outcomes after surgery or other painful conditions.

SHORT DUTCH SUMMARY

Nociceptie, ook ten gevolge van operatief ingrijpen, gaat gepaard met veranderingen in de werking van het perifere en centrale zenuwstelsel. Deze veranderingen, ook wel neuroplasticiteit genoemd worden beschouwd als een belangrijk mechanisme bij het ontstaan van zowel acute als chronische pijn na een operatie. Ofschoon de theoretische kennis gebaseerd op dierexperimenteel onderzoek waaruit blijkt dat biomoleculaire mechanismen en neuroplasticiteit met elkaar in verband staan aanzienlijk is toegenomen, blijft de klinische behandeling van chirurgische pijn een grote uitdaging. Aangezien een adequate behandeling van deze pijn mogelijk postoperatieve morbiditeit kan reduceren en de chirurgische resultaten kan verbeteren, is het van belang deze uitdaging aan te gaan.

Het lijkt logisch dat de behandeling van chirurgische pijn het meest succesvol zal zijn als deze gebaseerd is op kennis van de mechanismen betrokken bij de (chirurgische) nociceptie. Echter, op dit moment zijn bijna alle behandelingen van deze pijnklachten gebaseerd op subjectieve, klinische symptomen en metingen. Er is dus een duidelijke behoefte aan de ontwikkeling van objectieve, klinisch bruikbare metingen waarop men de overgang van een symptoom georiënteerde naar mechanisme gerichte pijnbehandeling kan baseren. Het doel van dit onderzoek is daarom de basis te leggen voor deze overgang door nociceptieve neuroplasticiteit te valideren als een objectief en bruikbaar eindpunt voor de gevolgen van chirurgische nociceptie en therapie.

Wij hebben deze vraagstelling op een aantal verschillende manieren benaderd. In sectie II wordt de theoretische achtergrond voor dit onderzoek weergegeven. Wij presenteren resultaten van dierexperimenteel onderzoek welke nociceptie, biomoleculaire mechanismen en neuroplasticiteit met elkaar in verband brengen (hoofdstuk 2). Verder worden de praktische aspecten van het meten van nociceptieve neuroplasticiteit door kwantitatieve sensorische toetsing (QST) en ook de relaties tussen QST en pijn besproken (hoofdstuk 3). Een gedetailleerd plan en de redenen voor het onderzoek worden gepresenteerd in hoofdstuk 4.

In de volgende twee secties (secties III-IV) worden de resultaten en toepassingen gepresenteerd van ons onderzoek waarin QST wordt gebruikt voor de kwantificering van analgesie en chirurgische neuroplasticiteit. Ten eerste (sectie III) valideren wij QST om de veranderde sensorische verwerking te meten in relatie tot het effect van analgetica. Hier worden studies geïntroduceerd die de antinociceptieve eigenschappen van zowel intraveneuze anesthetica (hoofdstuk 6) als ook opioide analgetica (hoofdstuk 7) teweegbrengen via QST door thermische of elektrische stimulatie. Vervolgens, in sectie IV, worden de resultaten van ons systematisch onderzoek over chirurgische nociceptieve neuroplasticiteit met QST gerapporteerd (hoofdstukken 10-15). Op basis van deze studies met meer dan 200 patiënten demonstreren wij de uitvoerbaarheid van QST in de klinische context. Bovendien wordt aangetoond dat het gebruik van de objectieve eindpunten van nociceptieve neuroplasticiteit nieuwe informatie geeft welke klinisch bruikbaar is en niet op andere manieren zoals door subjectieve pijn metingen verkregen kan worden

(samenvatting in hoofdstuk 16). In het bijzonder wordt aangetoond dat chirurgische nociceptie gevolgd wordt door een complexe neuroplastische reactie die in de tijd varieert en die zowel excitatie als ook inhibitie van spinale en supraspinale systemen betreft. Van belang is het feit dat preoperatieve pijn ook geassocieerd is met neuroplasticiteit. Deze zogenaamde inhiberende neuroplasticiteit welke acute preoperatieve ischialgie ("sciatica") begeleidt, kan vervolgens postoperatieve excitatoire neuroplasticiteit over een periode van 5 dagen reduceren. Perioperatieve analgesie oefent in het algeheel een positief effect uit op het reduceren van excitatoire postoperatieve neuroplasticiteit. Echter de exacte effecten hangen af van het toegediende medicament, de wijze van gebruik en de tijdsduur. Postoperatieve neuroplasticiteit wordt alleen beperkt en incompleet weergegeven door klinische pijn metingen zoals pijn scores of het gebruik van analgetica.

De laatste twee secties (secties V-VI) behandelen praktische toepassingen en implicaties van QST en nociceptieve neuroplasticiteit voor de behandeling van chirurgische pijn en nociceptie. Sectie V omvat twee overzichtsartikelen die de invloed van het concept van nociceptieve neuroplasticiteit bespreken zowel met betrekking tot de langdurig aanhoudende discussie over "pre-emptive analgesia" (hoofdstuk 17) als met betrekking tot praktische aspecten van QST gebruik in de chirurgische context (hoofdstuk 18). Samenvattend bespreekt hoofdstuk 19 de huidige en toekomstige vragen over de praktische uitvoerbaarheid en de effecten van QST en nociceptieve neuroplasticiteit op de praktijk van de perioperatieve behandeling van pijn. QST kan *nu* haalbaar geïntroduceerd worden in de klinische praktijk als een manier om nociceptieve neuroplasticiteit objectief te meten om zo een begin te maken van de overgang van een symptoom georiënteerde naar een mechanisme gerichte pijn behandeling.

In de toekomst zal meer gebruik gemaakt moeten worden - zowel in onderzoek als klinische praktijk - van deze unieke mogelijkheid om informatie te verkrijgen welke niet door klassieke subjectieve pijn metingen verschaft kan worden. Wanneer die situatie is bereikt zal de modulatie van nociceptieve mechanismen, met als doel een verbetering van de chirurgische resultaten en het vermijden van chronische pijnklachten, een veelbelovende toepassing van deze techniek kunnen zijn.

VIII

APPENDICES

22. CURRICULUM VITAE: OLIVER HAMILTON GOTTWALDT WILDER-SMITH

Oliver Wilder-Smith was born January 23, 1956 in Frankfurt/Main, Germany. After completing his schooling in England he went on to study medicine at Liverpool University Medical School in England from 1975 onwards, graduating M.B.,Ch.B. in 1980. After completing his housemanship at Walton Hospital in Liverpool, England, he went on to do his anaesthesiology speciality training in Germany at Berufsgenossenschaftliche Unfallklinik, Frankfurt/Main and Klinikum der Philipps-Universität, Marburg, receiving his specialty qualification in anaesthesiology (Arzt für Anaesthesiologie) in 1986. In the mean time he also obtained his M.D. from J.-W. Goethe Universität, Frankfurt/Main with a dissertation on spinal anaesthesia in 1985. After staff positions in Germany and Switzerland (Ulm University Hospital, Germany and Zieglerspital Bern, Switzerland), he moved to Geneva University Hospital, Switzerland for subspecialty training in pain and neuronaesthesia in 1991. From 1993 onwards he was chef de clinique scientifique there, and also built up their neuroanaesthesia unit. In 1996, Oliver Wilder-Smith became director of the Nociception Research Group, Berne University, Switzerland; during 1998-99 he was also consultant anaesthesiologist at Haukeland University Hospital in Bergen, Norway. Since 2001, he has been consultant in anaesthesiology and pain medicine at the University Medical Centre St. Radboud, Nijmegen, Netherlands.

Oliver Wilder-Smith is at present president of the European Association of Pain Researchers (EuroPain) and chairman of the EuroPain working party on acute nociception. He is member of many professional organisations including the German and French neuroanaesthesia groups (ADNANI, ANARL) as well as various international anaesthesia (ESA, ESRA, IARS) and pain (IASP, EuroPain, SGSS) societies. He has published over 60 articles in international peer-reviewed journals, has contributed a number of book chapters and review articles, and regularly reviews for journals in pain and anaesthesiology. He is happily married to Elly with whom he enjoys travelling and lecturing.

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