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ORIGINAL INVESTIGATION

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Interactions of the subthalamic nucleus and the subpallidal area in oro-facial dyskinesia: role of GABA and glutamate

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Abstract Previous studies have shown that lowering the GABAergic activity in the sub-pallidal area (SP) in the cat results in the display of oro-facial dyskinesia (OFD). There exists an intense, mutual anatomical connection between the SP and the subthalamic nucleus and the adjoining lateral hypothalamic area (STH). The present study investigated whether the STH is also involved in OFD. Once this turned out to be true (see below), it was investigated whether the SP-specific OFD is funneled via the STH, or vice versa. Bilateral injections of low doses (50–250 ng) of picrotoxin, a non-competitive GABA antagonist, into the STH were found to elicit OFD. This effect which was quantified in terms of numbers of tongue protrusions, was dose-dependent: a bell-shaped dose-response was found (50–500 ng). The OFD elicited by the most effective dose of picrotoxin (250 ng) was significantly antagonized by muscimol, a specific $GABA_A$ agonist, in a dose (50 ng) which itself was ineffective, indicating GABA specificity. In addition, it was found that OFD elicited by local injections of picrotoxin (250 ng) into the STH was significantly attenuated by SP injections of the broad spectrum glutamate antagonist kynurenic acid in a dose (1000 ng) which itself was ineffective, but not by muscimol (100 ng), indicating that the STH-elicited OFD needs an intact and functioning glutaminergic, but not GABAergic, transmission process in the SP for its expression. Finally, it was found that OFD elicited by picrotoxin injections (500 ng) into the SP was significantly attenuated by muscimol injections (50 ng) into the STH, indicating that the SP-elicited OFD needs an intact and functioning GABAergic transmission process in the STH for its expression.

Key words Oro-facial dyskinesia · Subthalamic nucleus · Globus pallidus · GABA · Glutamate · Behaviour · Cat

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Introduction

Oro-facial dyskinesia (OFD) is a syndrome of abnormal involuntary movements of the oral and facial muscles. It can occur in a variety of medicated and unmedicated subjects, but is predominantly present in patients chronically treated with antipsychotic or antiparkinson drugs (Schonecker 1957; for review: Waddington 1989). It has been hypothesized that OFD is due, at least in part, to alterations in dopaminergic systems (Klawans et al. 1980), although it is generally accepted now that it cannot simply reflect supersensitivity of dopamine receptors (Waddington 1989). GABA has also been suggested to play a crucial role in this syndrome (Fibiger and Lloyd 1984). However, the underlying neuronal mechanisms of OFD are still poorly understood, although the introduction of newly developed animal models have greatly increased the understanding of oral motor control (Ellison et al. 1987; Koshikawa et al. 1989; Prinssen et al. 1992).

In the cat it has been shown that OFD can be elicited by stimulating dopamine receptors within the anterodorsal part of the caudate nucleus (Cools et al. 1976; Spooren et al. 1991a). This part of the caudate nucleus (CN) is predominantly innervated by the cell group A8 and is characterized by a relatively low content of striosomes (Desban et al. 1989; Spooren et al. 1991a). OFD in the cat is also elicited from the first order output station of the CN, i.e. a circumscribed (enkephalin rich) part of the subpallidal area (SP; Cools et al. 1989a, b; Spooren et al. 1989; 1991b). Moreover, it has been shown that striatally-induced OFD can be blocked at the subpallidal level (SP), indicating that effects elicited from the CN are funneled through subpallidal structures (Spooren et al. 1991a).

Using *Phaseolus vulgaris* leucoagglutinin (PHA-L) as an anterograde tracer, we have recently shown that the dorsomedial part of the subthalamic nucleus and the adjoining lateral hypothalamic area (STH) receive a massive input from the OFD-sensitive subpallidal

region (SP; Spooren et al. 1993). The relationship of the subpallidal regions with the subthalamic nucleus is reciprocal in rat and monkey (rat: Berendse and Groenewegen 1990; monkey: cf. Russchen et al. 1985; Smith et al. 1990; Haber et al. 1993). Until recently, the subthalamic nucleus was thought to exert an inhibitory effect on the basal ganglia, but this view has changed dramatically over the last few years. It is accepted now that the output neurons of the subthalamic nucleus use glutamate as a neurotransmitter and exert a general excitatory influence upon their targets, among others the pallidal complex, and thus act as a "driving force" of the basal ganglia (Smith and Parent 1988; Albin et al. 1989; Bergman et al. 1990; Robledo and Feger 1990; Brötchie and Crossman 1991). In addition, recent data have indicated that subthalamo-pallidal and striato-pallidal projections converge onto the same pallidal neuron, having resulted in the hypothesis that the functional state of each pallidal neuron is determined by a complex interplay of excitatory and inhibitory inputs originating from subthalamic and striatal neurons, respectively (Hazrati and Parent 1992; Parent and Hazrati 1993; cf. Turski et al. 1990; Ryan and Clark 1991).

In view of these and other findings (see also: Crossman et al. 1984; Crossman 1987), the question arose to what extent the STH is involved in the control and/or expression of the OFD that originates in the CN and is funneled to the SP. The first series of experiments was devoted to the question whether the STH itself is involved in OFD. For that purpose, bilateral injections of the non-competitive GABA antagonist picrotoxin (PTX) were administered into the STH of freely moving cats. This drug was chosen in view of the fact that the major input to the STH is known to be a GABAergic projection from pallidal structures (Kim et al. 1976; Fonnum et al. 1978; Rouzaire-Dubois et al. 1980; Carpenter et al. 1981a, b). The behaviour was qualitatively and quantitatively analyzed in terms of numbers of the movements of the tongue, ear, eyelid and cheek. To establish the GABAergic nature of the PTX effects, two sets of experiments were performed: (a) a dose-effect curve was constructed, and (b) the ability of the $GABA_A$ agonist muscimol (MSM) to attenuate the PTX effects was investigated. Following the finding that the STH is indeed involved in the display of OFD, it was investigated (a) whether the OFD elicited from the STN needs the SP for its expression, and (b) whether the OFD elicited from the SP needs the STN for its expression. To answer the first question, we investigated to what extent bilateral injections of the glutaminergic antagonist kynurenic acid (KYN) or the $GABA_A$ agonist MSM into the SP could inhibit the OFD elicited by PTX injections into the STH. The glutamate antagonist was chosen in view of the fact that the transmission in the subthalamo-pallidal pathway is mediated by an excitatory amino acid, probably glutamate (see above). The GABA agonist was chosen in view of the fact that stimulation of GABAergic transmission in the SP is known to attenuate OFD elicited from the SP (Spooren et al. 1991a). To answer the second question, we investigated to what extent bilateral injections of the $GABA_A$ agonist MSM into the STH could inhibit the OFD elicited by PTX injections into the SP. The rationale for using the GABA agonist was two-fold: (a) the pallido-subthalamic pathway is GABAergic (see above), and (b) this drug was found to attenuate OFD elicited from the STH (outcome first series of experiments).

Materials and methods

Subjects and surgical procedures

Male cats ($n = 22$; age 12–13 months; Animal Laboratory, University of Nijmegen) weighing 3.5–5.4 kg were used. Each group, composed of seven or eight cats, was housed in a cage ($2 \times 3 \times 2$ m) with water and food available ad libitum and treated according to the (ethical) guidelines of the Dutch law on laboratory animals. Under deep anaesthesia [40 mg/kg pentobarbital (Narcovet, intraperitoneally; Apharmo, The Netherlands)] the animals were stereotaxically equipped with stainless steel guide cannulae (inner diameter and outer diameter 0.55 and 0.8 mm, respectively) aimed at the sub-pallidal area (SP: coordinates A 15.0, L 5.3, H −2.5, α lateral 7.0°, α caudal 5.0°; Snider and Niemer 1964) and/or the medial subthalamic nucleus and adjoining lateral hypothalamic area (STH: coordinates A 8.0, L 3.4, H −4.0; Snider and Niemer 1964). In order to avoid unnecessary damage to the target site, the cannulae were placed 2 mm above the target region.

Apparatus

Cats were tested in a soundproof observation cage ($90 \times 60 \times 60$ cm) with a Plexiglas front panel. The cage was equipped with two ventilators which produced a constant background noise.

Experimental procedures

After recovering from the operation for a minimum period of 3 days, the cats were placed in the observation cage to habituate them to the cage and to the experimental procedures (see below; each cat 3×1 h sessions on successive days). During the last habituation session the cats received a bilateral "dummy" injection. The experiments started after a minimum period of 7 days following the operation.

On the test day the cat was placed in the observation cage and allowed to rehabituate for a period of 15 min. The recording of the behaviour started immediately at the end of this period. The behaviour was recorded with the help of a closed circuit TV and stored on videotape for off-line analysis. The presence of oro-facial dyskinesia was detected by analyzing the nature of movements of the ear, eyelid, cheek and tongue. Oro-facial dyskinesia was quantitatively analyzed by counting the number of tongue protrusions which are known to signal the end of an OFD attack (Cools et al. 1989a). The experiment itself was divided into two parts by the injections: a pre-injection period of 15 min and a post-injection period of 45 min. The pre-injection period was used to discard animals that displayed abnormal tongue protrusions as a consequence of previous treatments. Since this only occurred in cats that received more than six drug treatments, the number of treatments was limited to six (Cools et al. 1989a). When cats received injections into different

structures, the injections known to elicit OFD were given immediately after the injections expected to attenuate OFD. All injections were given with a Hamilton syringe (5 µl; sharpened tip). The needle was lowered 2 mm below the end of the cannula in order to reach the chosen target site (see above). The injection itself lasted 15 s whereas the needle was kept in place for another 10 s.

Experiment 1

In this experiment eight cats equipped with cannulae directed towards the STH were used. They received the following bilateral injections: solvent, picrotoxin (PTX (Serva, Heidelberg, Germany): 250, 500, 50 and 150 ng, subsequently), muscimol (MSM (Serva, Heidelberg, Germany): 50 ng) and the combination PTX (250 ng) and MSM (50 ng) in a cocktail.

Experiment 2 and 3

In these experiments nine cats equipped with cannulae directed towards the STH and SP were used. They received bilateral injections of the following combination of drugs (SP–STH): solvent–solvent, solvent–PTX (250 ng), MSM (100 ng)–PTX (250 ng), PTX (500 ng)–solvent, PTX (500 ng)–MSM (50 ng) and kynurenic acid (KYN (Sigma, St Louis, USA): 1000 ng)–PTX (250 ng). An additional group of five cats were used to determine the effects of KYN injections alone into the SP. All drugs were dissolved in sterile distilled water (NPBI, The Netherlands), except for KYN which was dissolved in 1 N NaOH (pH correction and set on 7.4). All drugs were injected in a volume of 0.5 µl.

Histological evaluation

At the end of the experiments the cats were deeply anaesthetized with pentobarbital (60 mg/kg, intraperitoneally) and transcardially perfused with saline followed by a 4% paraformaldehyde solution. The brains were removed and subsequently cut on a freezing microtome in sections of 30 µm. The sections were stained for cresyl violet in order to estimate the location of the injection site.

Statistics

An overall Friedman two-way ANOVA was performed, followed by the Wilcoxon matched-pairs signed-ranks test (two tailed) or the Mann-Whitney *U* test (two-tailed). The latter was used in the case of independent groups design which only existed in the comparison of KYN injections alone (for which we used an additional group of animals; see above) with the other drug tests of experiments 2 and 3.

Results

Experiment 1

Histological data

Histological evaluation revealed that all injection sites were correctly placed into the target region of the STH as determined by the afferent input from the OFD-sensitive part of the sub-pallidal area [SP; Fig. 1 (cf. Spooren et al. 1993b)].

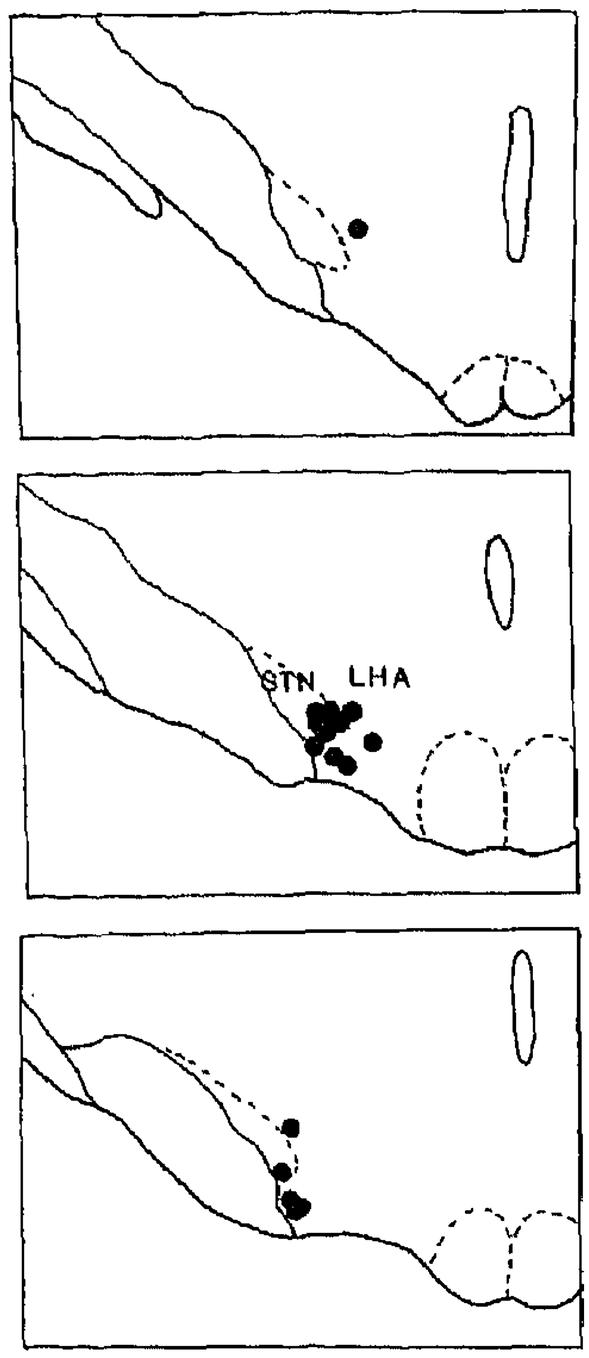

Fig. 1 The distribution of the injections sites in the STH from rostral (*top*) to caudal (*bottom*) levels of the cats used in experiment 1. One *dot* represents one injection site whereas all injection sites are represented on one side of the brain. Abbreviations: *STN* nucleus subthalamicus, *LHA* lateral hypothalamic area

Behavioural effects

Picrotoxin (PTX) in the dose range 50–250 ng elicited a full-blown oro-facial dyskinetic syndrome which consisted of sudden attacks of tic-like contractions involving the ear, eyelid and cheek which were accompanied by tongue protrusions. The tongue protrusions were abnormal and consisted of curling upwards the lateral sides of the tongue and protruding the curled tongue via the left or right corner of the mouth, or curling the tip of the tongue upwards and inwards against the palatum and then protruding it or pressing the tip of the tongue against the innerside of the cheek and then protruding it. Similar combinations of movements were previously seen in cats with OFD elicited from the anterodorsal caudate nucleus or the SP (Cools et al. 1976, 1989a). At the highest injected dose of PTX (500 ng) a combination of immobility and explosive motor activity was elicited. Seizures did not occur. For the longestpart of the observation the cats remained in a fixed position (immobile), standing, sitting or in a position between these two extremes. All animals had a trunk torsion, and their heads were either turned to a lateral side (lateral torticollis) or turned backwards (retro-torticollis). These positions were suddenly interrupted by moments of jumping and falling of the animal. All animals displayed a fixed facial expression

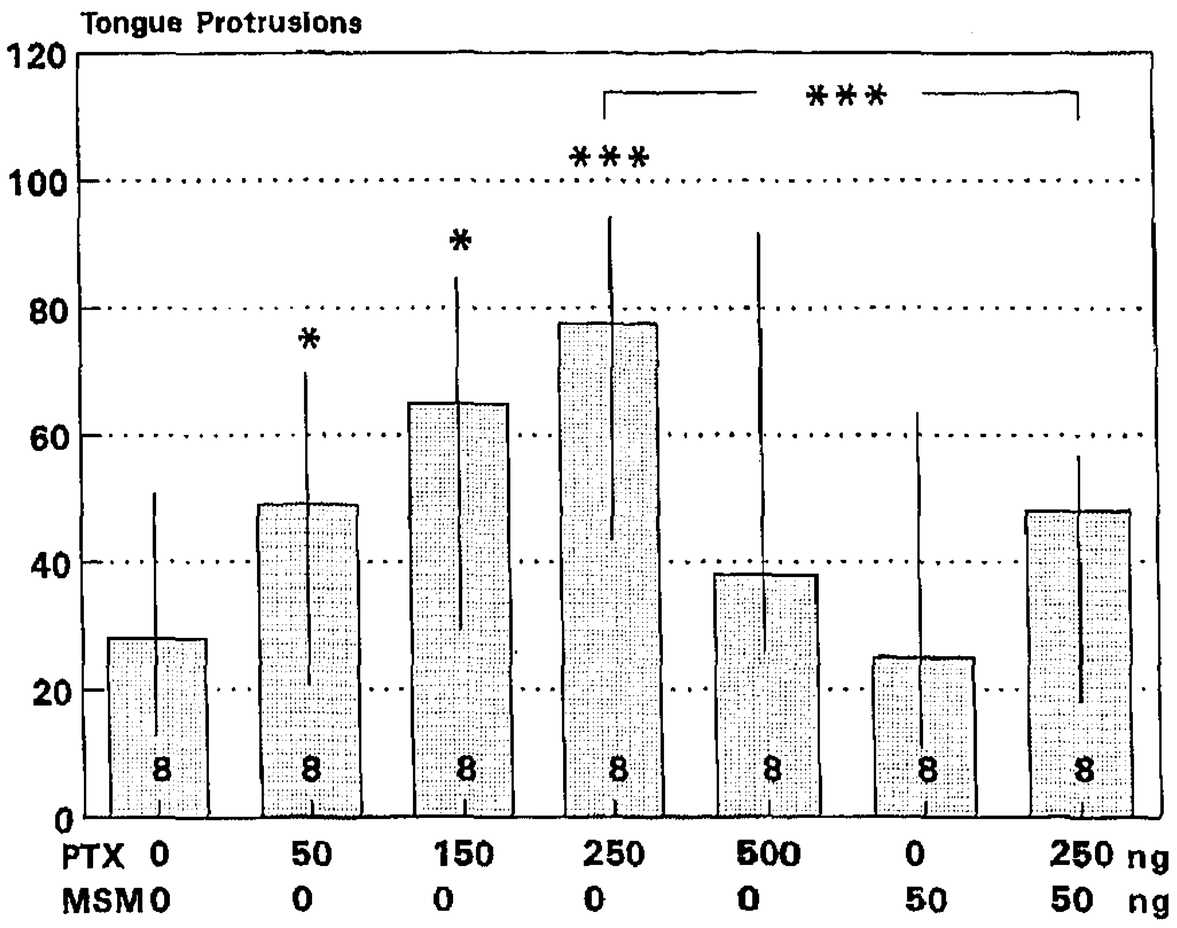

Fig. 2 Median value of the number of tongue protrusions in 45 min following bilateral injections of control [distilled water (*PTX*/*MSM*: O/O)], picrotoxin (*PTX*: 50, 150, 250 and 500 ng), muscimol (MSM: 50 ng) and the combination picrotoxin (PTX 250 ng) and MSM (50 ng) into the STH; bars in histograms represent the interquartile range (25–75%). Statistics: [Overall (0–500 ng PTX): Friedman two-way ANOVA ($\chi^2(4) = 9.5$, $P < 0.05$)]; (drug/dose specific comparison) Wilcoxon matched pairs signed ranks test, $^*P < 0.05$, $^{**}P < 0.02$, $^{***}P < 0.01$. (*ng* nanogram)

during which the corners of the mouth were pulled towards the ears. Only an incidental single burst of OFD was seen in these cats.

Quantitative effects

Dose-response relation. Bilateral injections of PTX (50, 150, 250 ng/0.5 µl) elicited a significant and dose-dependent increase in the number of tongue protrusions. The most effective dose was 250 ng, whereas a dose twice as high lost its efficacy [(0–500 ng PTX): Friedman two-way ANOVA ($\chi^2(4) = 9.5$, $P < 0.05$)]; a bell-shaped dose-response relation was the result (Fig. 2).

GABA specificity. The most effective dose of PTX (250 ng) was selected to determine GABA specificity: the number of tongue protrusions elicited by 250 ng PTX was significantly attenuated by 50 ng muscimol, i.e. a dose which itself had no effect (Fig. 2).

Experiments 2 and 3

Histological data

Histological evaluation revealed that all injection sites were correctly placed into the target region of the SP (Fig. 3a) and the STH (Fig. 3b).

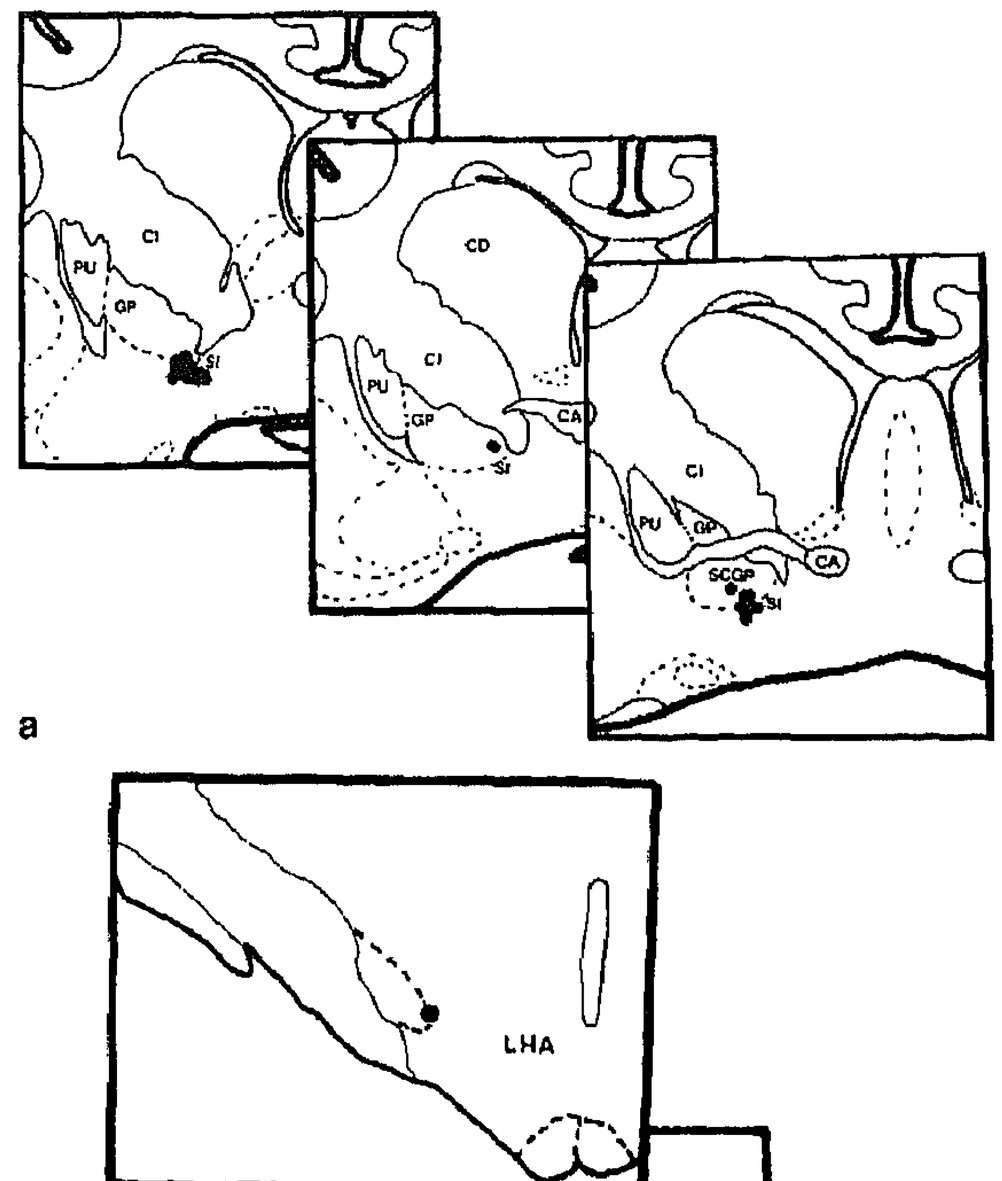

Fig. 3 The distribution of the injection sites in the SP (**a**) and the STH (**b**) of the cats used in experiments 2 and 3. One *dot* represents one injection site whereas all injection sites are represented on one side of the brain. Abbreviations: *CA* anterior commissure, *CD* caudate nucleus, *CI* internal capsule, *GP* globus pallidus, *PU* putamen, *SCGP* subcommissural part of the globus pallidus, *SI* substantia innominata

Involvement of glutamate and/or GABA in the SP following OFD elicited from the STH

PTX (250 ng) injected into the STH elicited a significant increase in the number of tongue protrusions (as described above; Fig. 4). This effect was in turn significantly attenuated by local injections of 1000 ng kynurenic acid (KYN), i.e. a dose which had no effect itself (Fig. 4), into the SP. In contrast, local injections of 100 ng MSM into the SP had no effect on the OFD elicited by 250 ng PTX in the STH.

Role of STH in GABA-mediated OFD in the SP

PTX (500 ng) injected into the SP, as outlined previously, elicited a full blown oro-facial syndrome which

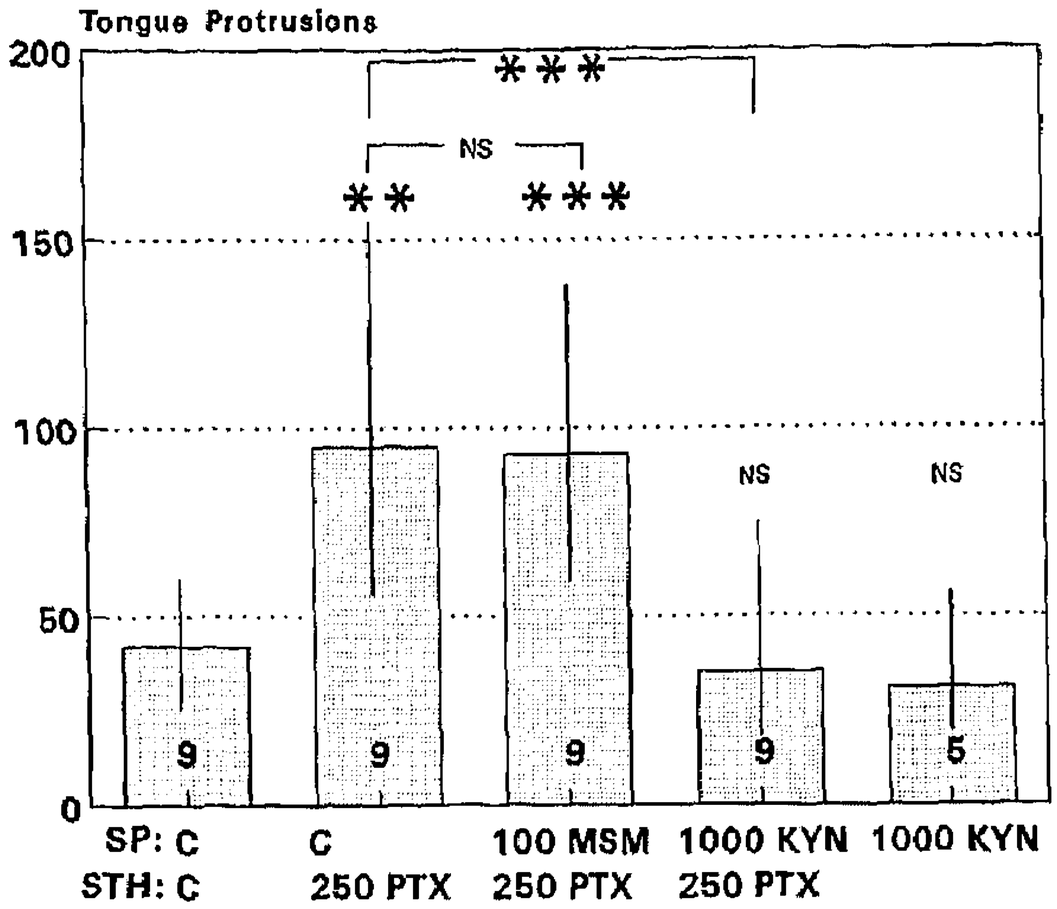

Fig. 4 Median value of the number of tongue protrusions in 45 min following bilateral injections of various drugs into the SP [muscimol (*MSM*); kynurenic acid (*KYN*) or their solvent (*C*)] and the STH [picrotoxin (*PTX*) or its solvent (*C*)];*bars* in histograms represent the interquartile range (25%–75%). Statistics: Wilcoxon matched pairs signed ranks test, $*P < 0.05$, $**P < 0.02$, $***P < 0.01$ (KYN injections alone were compared using the Mann-Whitney *U* test; see Materials and methods). Dose given in nanograms (*ng*)

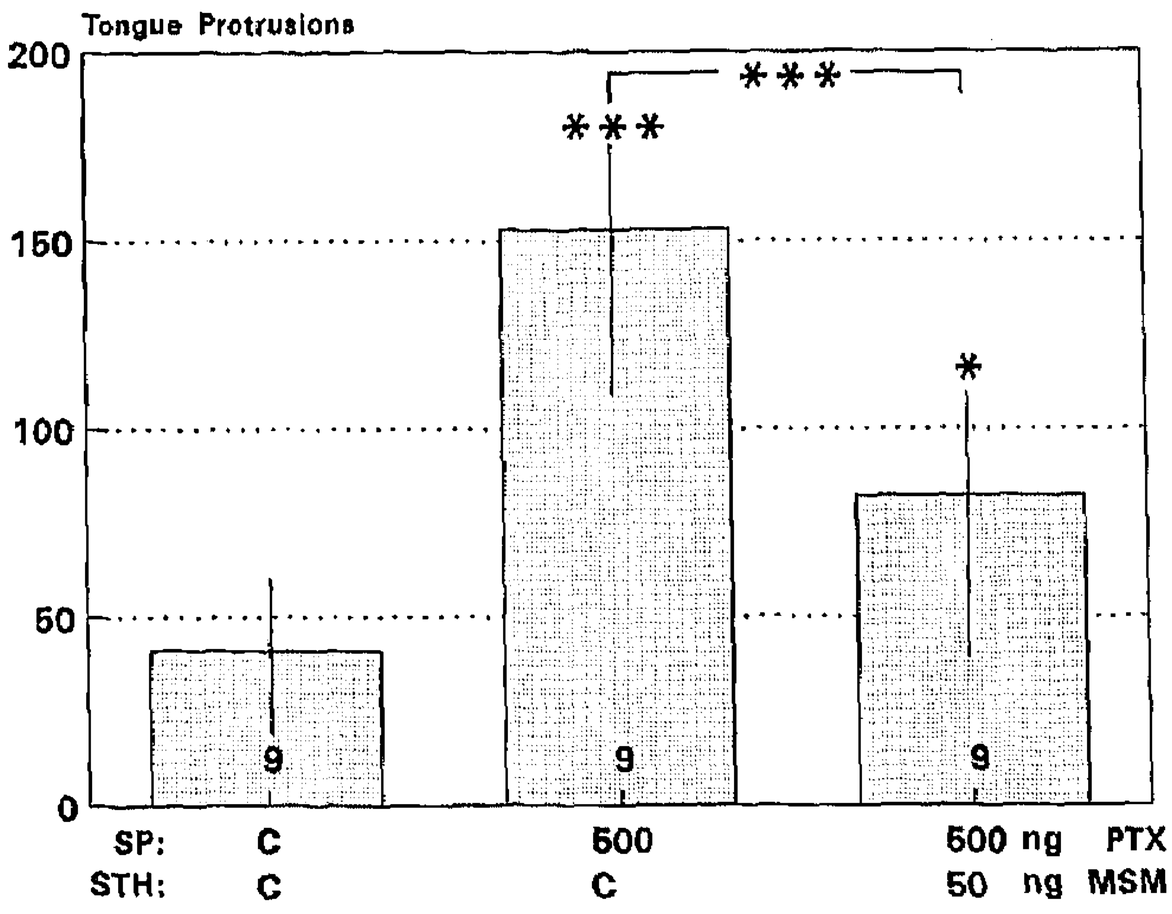

Fig. 5 Median value of the number of tongue protrusions in 45 min following bilateral injections of drugs into the SP [picrotoxin (*PTX*)] and the STH [muscimol (*MSM*)] or their solvent (*C*); *bars* in histograms represent the interquartile range (25–75%). Statistics: Wilcoxon matched pairs signed ranks test, $*P < 0.05$, $**P < 0.02$, $***P < 0.01$. *ng* nanogram

resulted in a significant increase in the number of tongue protrusions (Fig. 5). This effect was in turn significantly attenuated by local injections of 50 ng MSM, i.e. a dose which had no effect itself (Fig. 2), into the STH (Fig. 5).

Discussion

This study investigated the involvement of the medial part of the subthalamic nucleus and the adjoining lateral hypothalamic area (STH) in oro-facial dyskinesia (OFD) and the interaction of the STH with the OFD-sensitive subpallidal area (SP) in the cat. The main findings are detailed below.

First, the qualitative analysis of the behaviour elicited by local injections of low doses (50–250 ng/ 0.5 µl) of the non-competitive GABA antagonist picrotoxin (PTX) into the STH showed that the STH is involved in the display of OFD. The more lateral parts of the subthalamic nucleus were not investigated in the prevent study. However, since these parts of the nucleus do not receive input from the OFD-specific region of the SP (Spooren et al. 1993b), which is densely enkephalin immunoreactive (Cools et al. 1989b; Spooren et al. 1989) but also contains substance-P immunoreactive elements (cf. Groenewegen and Russchen 1984), it is unlikely that OFD is elicited from these parts of the subthalamic nucleus. The OFD seen in the present study did not differ from that seen in earlier studies on the involvement of the CN and the SP in OFD (Cools et al. 1989a; Spooren et al. 1991a, b). A quantitative analysis of the observed OFD showed that the effect was dose-dependent (50–250 ng). The observation that the highest dose of PTX (500 ng) induced a fully different syndrome, namely a combination of immobility and explosive motor activity, may indicate that the diffusion of PTX was no longer limited to the area under investigation. The $GABA_A$ agonist muscimol (MSM) was found to attenuate significantly the OFD elicited by the most effective dose of PTX (250 ng), whereas MSM alone did not produce any change in this respect. These data together show that the OFD under study was GABA specific. Thus, it is concluded that inhibition of GABA in the STH gives rise to OFD in the cat. Given the inhibitory nature of GABA, the present data imply that neurons of the STH are under inhibitory control of GABA under normal conditions. Since the STH receives a massive GABAergic input of the SP, it is most likely that the SP exerts this inhibitory control upon the STH. Previously it was shown that removal of the inhibitory control of GABA in the SP also results in OFD (Cools et al. 1989a, b). Combining both sets of data results in the notion that the removal of the inhibitory control by GABA in the SP did not disinhibit the GABAergic pallido-subthalamic pathway. Such a disinhibition would have led to an enhanced release of GABA in the STH which per se inhibits OFD (see below). Given the finding that enhancing the GABA activity in the SP prevents OFD elicited from the CN, it appears that the inhibitory control of GABA in the SP is exerted upon cells receiving a striatal input and not upon cells giving rise to the subpallido-subthalamic output. In any event, the available data show that OFD is under control of GABA in at least two distinct territories, i.e. subpallidal and subthalamic territories (cf. Gunne et al. 1984).

Second, the OFD effect of picrotoxin (250 ng) injected into the STH was significantly attenuated and

in fact completely blocked by injections of the broad spectrum glutamate antagonist kynurenic acid (KYN; 1000 ng), but not by the GABA agonist muscimol (MSM; 50 ng) into the SP. From these data it can be concluded that a) OFD elicited from the STH needs the SP for its expression and that b) this expression involves glutaminergic, but not GABAergic, transmission in the SP (see also below). Since the transmission of the subthalamo-pallidal pathway is mediated by an excitatory amino acid, probably glutamate (see introduction), it is likely that removal of this excitatory input underlies the suppression of OFD elicited from the STH. It was already known that enhancing the inhibitory control by GABA in the SP suppresses OFD elicited from the CN (Spooren et al. 1991a). In other words, there appears to exist a delicate glutamate-GABA balance in the SP that controls the presence or absence of OFD. The data also suggest that, apart from dopamine and GABA, glutamate too plays a role in the aetiology of OFD (cf. Andren and Gunne 1992).

Third, the OFD effect elicited by 500 ng picrotoxin injected into the SP was significantly attenuated by 50 ng muscimol injected into the STH. From these data it is concluded that a) OFD elicited from the SP needs the STH for its expression, and that b) this expression involves GABAergic transmission in the STH. Since the major input to the STH is a GABAergic projection from pallidal structures, it is likely that activation of this inhibitory input underlies the suppression of OFD elicited from the SP.

The present study shows that OFD is funneled along the pallidal-subthalamic-pallidal pathway and that, at least at this level of the brain, OFD remains within the boundaries of basal ganglia structures. However, the behavioural expression of this basal ganglia related disorder also involves participation of structures that are selectively innervated by basal ganglia regions. We recently have investigated the output structures of the SP which has led to the finding of several possible targets that may funnel the OFD from the SP to lower brain structures (Spooren 1992; Spooren et al. 1991c, 1993a, b). These include the lateral habenula nucleus, the central nucleus of the amygdala and the peripeduncular nucleus (Spooren 1992; Spooren et al. 1993a, b; unpublished observations). Recently we have shown that the peripeduncular nucleus is involved in oral motor control, but that this nucleus is not involved in the display of OFD (Spooren et al. 1993a). At present it is not clear along which neural circuits OFD is funneled.

In conclusion, the present study shows that inhibition of GABA in the STH induces OFD in the cat. This OFD effect needs the SP for its expression and is mediated via glutaminergic, but not GABAergic, neurotransmission. This study also shows that the OFD which is elicited from the SP needs the STH for its expression. This OFD effect is mediated via a GABAergic process in the STH.

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