

Stress Hormones, Genotype, and Brain Organization

Implications for Aggression^a

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INTRODUCTION

It is generally accepted that aggressive behavior is a specific feature of a more general pattern of stress reactions displayed by animals and humans in response to a changing environment, but how stress and aggression are related is not precisely known. Another fundamental question in stress and aggression research is why some individuals suffer from pathology, while others are healthy under seemingly similar conditions. Of great significance for the study of these questions are the seminal observations of Henry¹ and Engel,² which indicate that individuals with an extreme difference in stress reaction coexist in a normal population. In response to a psychosocial challenge, the extremists display either a fight/flight response³ or a conservation-withdrawal response. Individual differences in endocrine reactions that are associated with differences in aggressive coping styles have also been reported in other species than rodents, for example, tree shrews,⁴ monkeys,⁵ and humans.^{6,7}

In this contribution we will briefly review recent findings of studies with genetically selected mouse and rat lines that have substantiated the notion of coexistence of extreme differences in individual reaction patterns to stress. Next, we will address the issue that these individual differences not only depend on genotype, but also on the persistent effects of early experience related to mother-pup interaction. We focus on stress hormones, in particular on the corticosteroids, which, during ontogeny, program stress-reaction patterns for life. We conclude that the conceptual understanding of the underlying mechanism of hormone action in the nervous system has reached a sufficiently advanced level that new approaches are possible for studying the pathology of stress and aggression.

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GENETIC SELECTION FOR AGGRESSION AND SEROTONIN

Research by Bohus, Koolhaas, and colleagues⁸⁻¹⁰ has further substantiated the notion of the coexistence of two extremes in stress-reaction patterns. The Dutch researchers used for their studies two mouse lines genetically selected for aggressive behavior, that is, the aggressive short-attack latency (SAL) and the nonaggressive long-attack latency (LAL) mice. The SAL mice feature the fight/flight reaction mode. They are characterized by vigorous offensive aggression when confronted with an intruder, which turns into flight during confrontation with a physically stronger resident. By contrast, the LAL mice react with immobility and withdrawal.¹¹

Additional observations suggest that the variation in attack latency of the SAL and LAL mice seems to be a reflection of a more fundamental difference in the way these animals react upon their environment. Previously, it was shown that the SAL mice were more active in avoidance of an aversive experience (*e.g.*, electric shock) than LAL mice.¹² By contrast, the nonaggressive LAL animals show a passive behavioral response during threatening conditions.^{12,13} Furthermore, the SAL, rather than the LAL mice, rely, under stable living conditions, on behavioral routines; they perform worse and show a more impaired adaptation when conditions are changing. The SALs make, therefore, more errors than LAL mice in solving problems encountered during changes in maze configurations.¹¹ Accordingly, it is predicted that the SAL mice will be more successful in coping with challenge when settled in a territory under stable conditions, whereas the LAL mice have an advantage during migration.¹⁴ These LAL mice appear more flexible in adaptation to stress. If LAL mice choose passive behavior as an option to cope, this response is not an expression of "loss of control," but in fact a behavior that is essential for survival.

Active and passive animals also can be distinguished in neural and endocrine reaction patterns. The active behavioral response (fight/flight) pattern is characterized by high sympathetic activity, but the corticosteroid level is low, provided the subjects are successful. The passive behavioral strategy is characterized by high parasympathetic activity, and corticosteroids (CORT) remain high in subjects suffering from psychosocial defeats.^{9,15} The testosterone level is generally high in active and low in passive animals.^{16,17}

Recently, we have studied the serotonergic 1A (5-HT_{1A}) receptor in the brains of SAL and LAL mice. The aggressive SAL mice had a level of 5-HT_{1A} mRNA about twice as high in the dorsal hippocampus as observed in the LAL mice. Ligand binding studies showed that increased postsynaptic 5-HT_{1A} receptor expression was also reflected on the protein level in view of the increased 5-HT_{1A} receptor number in the dorsal hippocampus, lateral septum, and frontal cortex. However, no difference in presynaptic 5-HT_{1A} receptors in the dorsal raphe nucleus of SAL and LAL mice was found.¹⁸ Thus, postsynaptic 5-HT_{1A} receptor expression is high in SAL mice having a low CORT tone.

In rats, attacks, quite similar to the attacks of SAL mice, can be induced by pharmacological or electrical stimulation of a hypothalamic area that partly overlaps with the tuberoinfundibular hypothalamus.¹⁹ Interestingly, such attacks can be selectively inhibited by the dopaminergic antagonist, haloperidol, serotonergic agonists, and the serotonin reuptake inhibitor, fluvoxamine.^{19,20} Moreover, the same serotonergic drugs dose-dependently suppress the active coping component (biting and kicking) in "spontaneous" intermale aggression while leaving the rest of the social interactions unaffected.^{20,21}

Taken together, these data collected from studies with SAL and LAL mice suggest that genetic selection for aggressive behavior coselects for an active coping style, a relatively low corticosteroid hormone exposure, but high limbic 5-HT_{1A} receptor expression. In agreement with previous pharmacological studies using partial 5-HT_{1A} agonists (serenics, *e.g.*, eltoprazine) or 5-HT reuptake inhibitors with antiaggressive properties,²² the findings suggest a specific role for the limbic 5-HT₁ receptors in regulation of aggression.

GENETIC SELECTION AND DOPAMINE

Aggressive SAL mice show a greater enhancement of stereotyped behavior in response to apomorphine than nonaggressive LAL mice.²³ This observation is of particular interest, inasmuch as a series of experiments was recently completed using rats genetically selected for apomorphine susceptibility. In 1985, Alexander Cools of the Catholic University of Nijmegen, the Netherlands, initiated a breeding program based on pharmacogenetic selection of Wistar rats, using as a criterion stereotypic gnawing induced by the mixed dopamine (D₁/D₂) receptor agonist, apomorphine. Apomorphine-unsusceptible (apo-unsus) rats, which virtually lacked a gnawing response accounted for about 25% of the total population. Another 25% were apomorphine-susceptible (apo-sus), showing vigorous gnawing in response to the drug. The remainder of the population consisted of rats with an intermediate gnawing score. In each generation the most outspoken apo-sus and apo-unsus rats enrolled a particular breeding procedure to maintain genotypic heterogeneity.²⁴

Psychopharmacological studies suggested that the two rat lines represent the extremes in dopamine responsiveness coexisting in a normal rat population.²⁴ Rats of the two selected lines have considerable variation in behavioral and locomotor responses to stress. Apo-sus rats show fleeing behavior after decisive psychosocial defeat and increased locomotor activity in response to novelty.²⁴ Along with enhanced apomorphine susceptibility, coselection occurs in the apo-sus rats for an active behavior response adopted during coping with stress. Apo-sus rats show, therefore, many of the characteristics displayed by the SAL mice.

Apo-sus rats have significantly higher tyrosine hydroxylase mRNA (THmRNA) and D₂ receptor binding and D₁ receptor mRNA levels (D₂ receptor mRNA and D₁ receptor binding were not different) in the nigrostriatal and tuberoinfundibular pathway, thus providing a neurochemical basis to the line differences.²⁵ Prolactin release in response to stress is significantly lower in apo-sus rats than their apo-unsus counterparts, which is in line with the prediction from the increased tuberoinfundibular dopamine activity.²⁶ These findings suggest that the high susceptibility for apomorphine-induced stereotypy is reflected by increases in measures for central dopamine activity. The observations also suggest coselection for differential neuroendocrine reactivity in the two genetically selected lines.

Recent studies showed that under basal morning conditions apo-sus rats had a larger number of corticotropin-releasing hormone (CRH) gene transcripts in paraventricular nucleus (PVN) and a higher corticotropin (ACTH) level in plasma relative to their apo-unsus counterparts.^{26,27} However, similar concentrations of circulating CORT were observed in both lines. Subsequently, the line difference in sensitivity of the hypothalamic-pituitary-adrenal (HPA) axis to stress was tested by exposing rats to a novel environment. A relatively enhanced ACTH response was observed in apo-sus rats, suggesting that the sensitivity of the ACTH response

to stress was increased. Stress-induced CORT secretion did not show a line difference. In fact, the apo-sus adrenal required much higher ACTH levels to maintain the same total CORT level under basal and stress conditions. Thus, it appears that the apo-sus adrenal is hyporesponsive to ACTH.^{26,27}

Stress-induced ACTH levels in apo-sus rats remained elevated longer as compared to apo-unsus animals. Also the plasma total and free CORT levels were significantly elevated for longer time intervals after stress. This reduced the ability of apo-sus animals to terminate stress-induced ACTH, and free CORT responses are indicative of CORT feedback resistance relative to their apo-unsus counterparts. The possible site of this CORT resistance was evaluated by conducting humoral challenge tests of pituitary and adrenocortical function. There was no line difference in the CORT response to exogenous CRH and ACTH, suggesting that the feedback resistance of apo-sus rats resides in the brain.^{26,27}

In conclusion, genetic selection of rats for extreme differences in susceptibility of the dopamine system coselects for active versus passive behavioral responses during a challenge. In the neuroendocrine realm, coselection also occurs for extreme differences in stress-induced prolactin and ACTH as well as for corticosteroid feedback efficacy. Accordingly, the increased susceptibility to dopaminergic stimulation during stress is associated with decreased prolactin release and impaired containment of the HPA axis by corticosteroids due to adrenocortical hyporesponsiveness and neuroendocrine feedback resistance.

GENOTYPE, STRESS, AND AGGRESSION

Rat lines were also selected on the basis of fear-conditioned behavior. Roman high avoidance (RHA) rats show rapid acquisition of an avoidance response as opposed to the poorly performing Roman low avoidance (RLA) animals. RHA animals show an enhanced locomotor response to novelty, greater exploration, and more activity and aggression than do RLA rats.²⁸ RHA animals lack a stress-induced increase in plasma prolactin, have an enhanced ACTH response to stress, but display hyporesponsiveness of the adrenals relative to RLAs.²⁹ Thus, the selection criterion of avoidance behavior allows coselection for divergence in HPA and prolactin responses to stress.

Upon closer inspection a number of subtle differences are noticeable, confirming the obvious fact that, of course, not exactly the same populations are selected by avoidance behavior, attack latency, and apomorphine susceptibility. For instance, the data on feedback efficiency between the apo-sus and RHA animals do not match and require further study. Yet, the analysis of behavioral and neuroendocrine response patterns suggests that apo-sus, RHA animals, and SAL mice all represent the genetic selection of animals in the fight/flight, active, aggressive category. These subjects are characterized by highly offensive behavior in social confrontations, whereas their counterparts hardly display any aggression. Accordingly, a common genetic background of stress-reaction patterns, coping styles, and aggression is likely.

The two previous sections also emphasized enhanced postsynaptic nigrostriatal dopamine receptor and limbic serotonin receptor properties in aggression-prone rodents. In view of the genetic background of these altered amine receptor functions, it is of interest that, recently, knockout mice became available that had particular genes in amine signaling ablated. Mice with targeted disruption of the tyrosine hydroxylase gene (supplemented with L-dopa in utero) show impaired

motor functions due to deficient nigrostriatal dopaminergic pathways, but no data on aggressive behavior are available in these mutants.³⁰

Transgenic mice lacking monoamine oxidase (MAO)-A³¹ or 5-HT1B gene expression³² show increased aggressive behavior, reinforcing the notions on the genetic background related to the serotonin system in the manifestation of pathological aggression. Both mutants have in common that serotonergic transmission by way of postsynaptic 5-HT1A receptors is enhanced. This evidence from transgenesis is in line with the outcome of pharmacological and endocrine studies linking aggression with high serotonergic tone. The SAL mice have high limbic 5-HT1A receptor expression.¹⁸ High stress-induced CORT levels enhance serotonergic transmission in limbic pathways.³³⁻³⁵ Partial 5-HT1 agonists are anti-aggressive, and their action mechanism possibly involves postsynaptic 5-HT1A receptors.²²

EARLY LIFE EVENTS ALTER BRAIN DEVELOPMENT

Collectively, the previous sections provided strong evidence for a genetic component in precipitation of aggressive behavior. Yet, another line of research has provided increasing evidence for a decisive role of early experience in programming of circuits underlying stress-response patterns in adult life. Below we first outline the features of the developing stress system, and next we will review the impact of early experience. The progress in this field is due to the pioneering studies of Seymour Levine.³⁶ More recently, the contributions of Michael Meaney and colleagues (this volume) have been important for linking the 5-HT system³⁸ with stress hormones in shaping the brain's ability to manage stress.³⁷

Between postnatal days 4 and 14 the HPA axis in the rat is hyporesponsive to stress. During this stress-hyporesponsive period (SHRP) circulating CORT and ACTH levels are extremely low. Stressors that evoke a pronounced CORT response during adulthood are only weakly active in the infant. Corticosteroid-binding globulin (CBG) levels are not detectable during the SHRP, and the very low CORT levels are in the free form.³⁸

The cause of the diminished responsiveness to stress during the SHRP appears to be multifactorial and depends on specific internal (endocrine, neural) and external (maternal) inputs to maintain overall quiescence. The major rate-limiting factors in HPA activation appear at the level of the brain and the adrenal.³⁹ Under most conditions, however, acutely elevated ACTH or exogenously administered ACTH do not trigger an adrenocortical response. The proximal cause of the SHRP lies, therefore, at the level of the adrenal due to reduced sensitivity to ACTH.

Studies using maternal separation have demonstrated that the mother regulates HPA responses in the infant. These HPA responses slowly develop as a function of time after maternal separation. A normally reared pup does not display CORT responses to saline, novelty, and acute maternal separation, unless maternal deprivation is prolonged for at least 8, and up to 24, hours. The phenomenon appears to involve priming (sensitization) of the adrenal to ACTH and stress. Besides duration, also the age of the infant exposed to maternal separation causes effects on HPA activity. The ACTH and CORT responses to ether, novelty, and saline injection immediately following 24 hours of maternal deprivation are larger at 9, 12, and 16 days of age, than at day 3.^{36,40}

Maternal deprivation also revealed which factors actually are responsible for neonatal activation of the HPA axis during the SHRP. It appeared that tactile

stimulation suppresses neural pathways involved in suppression of ACTH release. Feeding has yet other effects, which are predominantly peripheral, as demonstrated from the enhanced adrenocortical responsiveness following maternal deprivation.^{36,41,42} Brief repeated daily separations (handling) followed by intensified sensory stimulation by the mother facilitates maturation of specific neural (limbic) pathways.^{36,37} By contrast, a single 24-h period of maternal deprivation evokes, during the SHRP, increased CORT at a time the hormone level otherwise would be low and unperturbed.

PERMANENT STRESS SYSTEM EFFECTS OF EARLY EXPERIENCE

During development, maternal behavior ensures a quiescent stress response system in the newborn rat, which is characterized by low and constant CORT levels. There is now convincing evidence that altered mother-pup interaction has the ability to alter brain development and, subsequently, behavioral and physiological responses in later life. We have known for many years that enhanced sensory stimulation evoked by the handling procedure advances the maturation of the stress system.^{43,44} During adulthood and senescence, handled animals show lower CORT levels in response to stress and improved cognitive functions in spatial learning.⁴⁵ By contrast, if daily separations are increased to 3 hours per day during the SHRP, the outcome for stress-induced HPA activation and cognition is the opposite. Such daily-deprived animals show hypercorticism and poor performance in spatial learning.⁴⁶

As pointed out in the previous section, recent research using the 24-h deprivation paradigm has revealed some aspects of the underlying mechanism responsible for programming the stress system. The disruption of the SHRP causes inappropriate high levels of CORT, which are thought to interfere with normal brain development. Steroid hormones have profound and permanent effects on the differentiating nervous system. Such permanent steroid effects persist in adulthood and senescence. This is known for testosterone. Administration of testosterone during postnatal days 2 to 4 masculinizes brain and behavior⁴⁷ (after intracellular conversion to estradiol), which has profound effects on aggression.

During development CORT administration has permanent effects on growth and differentiation of the brain. The steroid inhibits protein synthesis, glucose uptake, neurogenesis, and gliogenesis. Neuronal "birthdays" are altered, and myelinogenesis, formation of dendritic spines, axonal growth, and synaptogenesis are retarded.⁴⁸ CORT is critical for neurotransmitter phenotype. For instance, without glucocorticoid receptors (GR) (in the homozygous mutant with targeted disruption of GR), the adrenal medulla is poorly developed.⁴⁹

Thus, depending on the duration of maternal separation, the infant may experience changing effects of maternal sensory stimulation and/or CORT. As adults the consequence of short- and long-term maternal deprivation is strikingly different, inasmuch as emotional and adrenocortical reactivity seem oppositely affected. Other experiments have shown that the timing of the 24-h deprivation is also critical. The outcome of 24-h deprivation at three days of age is opposite of deprivation at 11 days, if ACTH levels at 20 days are taken as the index (van Oers, de Kloet, and Levine, manuscript in preparation). Deprivation at three days increases ACTH levels at 20 days.⁵⁰ As young adults (two months), the mother-deprived rats have reduced basal CRH mRNA expression. However, basal plasma ACTH and CORT levels are significantly elevated. Adrenal weight is also increased.⁵⁰

Long-lasting effects of maternal deprivation have also been found on CORT receptor levels. Twenty-four hours of deprivation at postnatal day three resulted in reduced GR mRNA in PVN and anterior pituitary and reduced hippocampal GR binding in male adult rats. The reduced GR expression in the PVN is consistent with the feedback resistance, whereas the ensuing hypercorticism would explain GR down-regulation in the hippocampus due to overexposure to the steroid.⁵⁰ Interestingly, adult female rats showed the opposite effect, and an increased hippocampal GR number was found after deprivation on day three.⁵¹ Sex differences were also noticed in rat pups exposed to endotoxin treatment on day three and analyzed as adults for basal and stress-induced HPA activation.⁵²

DOES A TRAUMATIC EARLY LIFE EVENT PROGRAM AGGRESSIVE BEHAVIOR?

This section is short, because, to our knowledge, in rodents there are no data that have directly addressed the question on aggressive behavior precipitated by early life events. Yet, the animal experiments described above provide evidence, allowing some speculation. In our experiments we showed that male rat pups deprived at postnatal day three showed as adults increased susceptibility for apomorphine, as judged from the increased stereotyped behavior after administration of the drug. These animals showed hypercorticism and increased nigrostriatal dopamine responsiveness.^{50,53} This finding raises the interesting point that the genetic selection for apomorphine susceptibility actually selects for a phenotype that is programmed by altered stress system activity due to the effect of early experience. Indeed, when the development of the nigrostriatal dopamine system and the HPA axis was examined in the apo-sus and unsus rat lines, HPA activity was increased after 20 days at a time dopamine was not affected.^{53,54}

These data show that there is conclusive evidence from experiments in rats that the early experience of maternal deprivation permanently affects stress regulation.^{45,50,55} The duration and frequency of the separation as well as the age and the sex of the pup appear to determine the outcome of the maternal deprivation procedures. The significance of these findings in relation to coping styles and aggressive behavior of the SAL, apo-sus, and RHA animals still needs to be explored.

CONCLUDING REMARKS

The idea that aggression may have a heritable basis touches upon fundamental scientific and social questions. The scientific questions concern the mechanisms of selection, the brain mechanisms involved, and the role of the developmental processes. The social questions concern strategies and time windows for prevention and intervention. It is generally assumed that aggressive behavior is caused by an interaction of biological, environmental, and social factors.⁵⁶ Therefore, it seems unlikely that a single gene would be responsible for the expression of aggressive behavior or that a particular gene would be exclusively involved in the expression of aggression. This concept is supported by the fact that selection on aggression also selects on active coping strategies accompanied by a typical endocrine phenotype in tree shrews,⁴ monkeys,⁵ and humans⁶ and is described in detail here for mouse and rat lines.

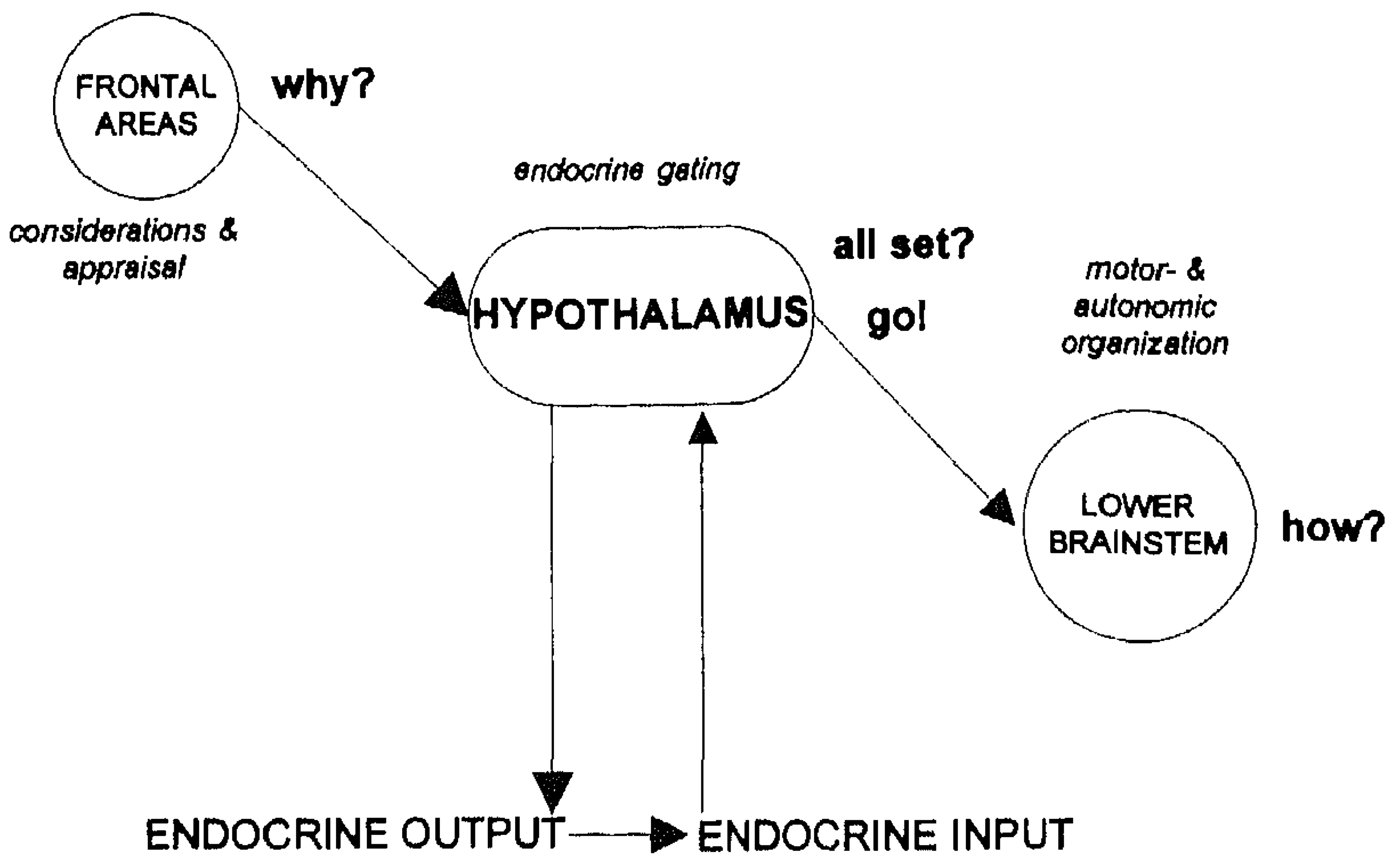


FIGURE 1. Functional integration scheme of the hypothalamus. The hypothalamus receives sensory input censored by the frontal areas, for example, frontal cortex, hippocampus, amygdala, septum, striatum, basal forebrain, and cerebral cortex. These areas contain neural circuits underlying appraisal of the sensory stimulus. The hypothalamus processes this information, and information processing depends on the neuroendocrine context. Lower brain-stem areas, for example, the substantia grisea centralis, ventral tegmental area, substantia nigra, formatio reticularis, and nucleus raphe anterior are involved in the organization of specific subroutines required for aggressive behavior.

In rats, very little work has been done on the HPA axis and aggression, as most work has concentrated on sex steroids and aggression.⁴⁷ However, it is known that CORT rises during fights in losers (intruders) and winners (residents)^{16,56,57} but that winners show a much more effective termination of the CORT response.¹⁶ Prolactin also rises, but mainly in losers, suggesting some defect in dopaminergic suppression (re, all aggressive mouse and rat lines had blunted prolactin responses). There is some evidence suggesting that CORT are involved in the expression of aggression in rats,^{58,59} inasmuch as hypothalamic implants of CORT dramatically increase aggression in golden hamsters.⁶⁰ Taken together, these findings clearly suggest that studying aggression as a component of more general coping strategies may be worthwhile, conceptually as well as experimentally. This view calls for studies in the neuroendocrine context (FIG. 1).

The recent study on a so-called "aggression gene" in humans⁶¹ can also be viewed as evidence for a linkage between aggressive behavior and general mechanisms involved in active coping with stressors. The males not only assault, but they are also rapists and arsonists. Moreover, the evidence presented shows that such aggressive episodes are often precipitated by failure to cope with perceived stressors.⁶¹ Interestingly, the aggression gene encodes for an enzyme (MAO-A) breaking down serotonin and noradrenaline. As pointed out previously, mutant mice having the MAO-A gene ablated display aggressive behavior as well.³¹

Retrospective studies have clearly established the effects of childhood abuse and neglect on adult violent and criminal behavior in humans. Yet, despite slogans like "violence begets violence" or "the cycle of violence," the majority of abused

and neglected children do not become violent.⁶²⁻⁶⁴ How such individual differences arise is not clear (why some individuals are more vulnerable than others) and cannot be easily assessed in humans. Consequently, studies are few, and defining vulnerable populations and successful intervention programs has been difficult.⁶⁴ However, in a recent study, Scarpa and Kolko⁶⁵ found that children who "internalized" their abuse experiences were more likely to become aggressive. This was especially the case in those children who responded with increased cortisol in saliva following a provocative computer task. These findings suggest that aggressive behavior arises as a result of an interaction of biological and developmental factors.

Developmental studies on the effect of early neglect, violence, and stress on aggressive behavior and brain mechanisms later in life are rare. The available knowledge on aggressive brain mechanisms may not allow such studies yet. However, conceiving aggression as a component of a mechanism involved in active coping with stressors may open new ways to study interactions between genetic background and early experience in aggression. The much more extensive knowledge of the neuroendocrine mechanisms involved in the response to stressors has made it possible to define specific developmental factors that affect behavioral and endocrine responsiveness later in life.³⁶⁻⁴⁴ A similar approach could be applied in aggression research, which would ultimately allow us to define windows of opportunity for more successful interventions and therapies.

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