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Neurobiological Mechanisms of Aggression and Stress Coping: A Comparative Study in Mouse and Rat Selection Lines

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Aggression · Amygdala · Behavior · Comparative studies · Corticosterone · Rodent · Septum · Serotonin · Stress · Vasopressin

Abstract
Aggression causes major health and social problems and constitutes a central problem in several psychiatric disorders. There is a close relationship between the display of aggression and stress coping strategies. In order to gain more insight into biochemical pathways associated with aggression and stress coping, we assessed behavioral and neurobiological responses in two genetically selected rodent models, namely wild house mice selectively bred for a short (SAL) and long (LAL) attack latency and Wistar rats bred for high (HAB) or low (LAB) anxiety-related behavior. Compared to their line counterparts, the SAL mice and the LAB rats display a high level of intermale aggression associated with a proactive coping style. Both the SAL mice and the LAB rats show a reduced hypothalamic-pituitary-adrenal (HPA) axis response to non-social stressors. However, when exposed to social stressors (resident-intruder, sensory contact), SAL mice show an attenuated HPA response, whereas LAB rats show an elevated HPA response. In both rodent lines, the display of aggression is associated with high neuronal activation in the central amygdala, but reduced neuronal activation in the lateral septum. Furthermore, in the lateral septum, SAL mice have a reduced vasopressinergic fiber network, and LAB rats show a decreased vasopressin release during the display of aggression. Moreover, the two lines show several indications of an increased serotonergic neurotransmission. The relevance of these findings in relation to high aggression and stress coping is discussed. In conclusion, exploring neurobiological systems in animals sharing relevant behavioral characteristics might be a useful approach to identify general mechanisms of action, which in turn can improve our understanding of specific behavioral symptoms in human psychiatric disorders.

Introduction

There is an increasing prevalence of excessive aggression, violence and terrorism in human society, which causes major health and social problems and is a costly burden on society. Aggressiveness is a key symptom in a large number of psychiatric disorders, including mood disorders (depression, post-traumatic stress disorder, intermittent explosive disorder) and personality disorders (conduct, antisocial and borderline personality disorders) [for review see Haller and Kruk, 2006]. There is a close relationship between aggression and the way humans (and animals) cope with stressors [Kruk et al., 2004]. The display of aggression or violence is often as-

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sociated with a strong emotional and physical arousal. Patients suffering from mood disorders mostly show a hyperarousal-driven aggression (associated with high autonomic responses, high glucocorticoid levels and high affective reactions), whereas patients with personality disorders show a hypoarousal-driven aggression (characterized by low affect, low autonomic responses to stress, low HPA hormone levels, and low skin conductance) [Haller and Kruk, 2006]. The former type of aggression might also be referred to as an impulsive-reactive-hostile-affective subtype, and the latter can be referred to as a controlled-proactive-instrumental-predatory subtype of aggression [Vitiello and Stoff, 1997]. These different features of aggression are important to distinguish normal from abnormal aggression and to define aspects of abnormal aggression in animal models.

A major challenge in clinical and preclinical aggression research is the identification of neural mechanisms that underlie aggressiveness. Despite the discovery of susceptibility genes, it is likely that complex disorders, such as aggressiveness, are influenced by multiple interactions of many genes with each single gene contributing only a small effect [Maxson, 1996; Craddock and Forty, 2006; van Belzen and Heutink, 2006]. Moreover, violence and aggression are most likely generated by a complex interaction of gene activity with environmental factors, in which in particular stressful situations play an important role. Thus, in order to reveal neurobiological pathways involved in aggression in relation to stress coping, appropriate animal models are needed. A classic approach is to investigate the regulation of natural forms of aggressive behavior, such as offensive, defensive, or maternal aggression [Blanchard et al., 2003]. To study abnormal aspects of aggression, several animal models have been developed, such as glucocorticoid hypofunction [Haller et al., 2001], olfactory bulbectomy [Leonard and Tuite, 1981], alcohol administration [Miczek et al., 1997], and frustrative non-reward [de Almeida et al., 2005]. These animal models are very useful in understanding specific aspects of abnormal aggression. As a complementary approach, animals selectively bred for extremes in behavior could be very useful to analyze genetic as well as neurobiological correlates of specific psychopathologies including aggressive disorders. In this review, we will assess and discuss behavioral and neurobiological responses in two independent animal models, namely male wild house mice selectively bred for either a short (SAL) or a long (LAL) attack latency and male Wistar rats bred for either high (HAB) or low (LAB) anxiety-related behavior.

SAL and LAL Mouse Lines

Male SAL and LAL mice, originating from a colony of wild house mice *(Mus musculus domesticus)* and maintained at the University of Groningen, the Netherlands, were selected based on their latency to attack a non-aggressive opponent male at the border of their home cage [van Oortmerssen and Bakker, 1981]. Attack latency is a reliable indicator of aggression in mice [Catlett, 1961; van Zegeren, 1980]. High aggression in the SAL mice correlates with the way these mice react to environmental challenges in general. For example, SAL mice show active behavioral responses when exposed to diverse stressors such as the shock-probe/defensive burying test [Sluyter et al., 1996a], the two-way shock avoidance test [Benus et al., 1989], and the forced swim test [Veenema et al., 2003a, b]. In contrast, LAL mice show high freezing/immobility when exposed to these tests. Furthermore, SAL mice are very rigid and habitual, whereas LAL mice are more flexible and respond more appropriately to changes in the environment [Benus et al., 1988, 1990, 1991]. Thus, SAL and LAL mice show distinct behavioral responses and represent the extremes of behavioral response patterns that coexist in a mammalian population [Henry and Stephens, 1977]. SAL mice are characterized by a 'proactive' coping style and LAL mice display a 'reactive' coping style [for review see Koolhaas et al., 1999].

HAB and LAB Rat Lines

Male and female HAB and LAB rats, originating from commercially available Wistar rats (Charles River, Sulzfeld, Germany), are genetically selected for differences in anxiety-related behavior on the elevated plus maze [Liebsch et al., 1998a]. Genetic selection started in 1993 and the lines were crossbred with rats from Leipzig breeding lines selected for high and low performance on an active avoidance task [Hess et al., 1992] to improve fitness and to reinforce line differences in anxiety-related behaviors. To study the relationship between the innate level of anxiety and coping strategy, LAB and HAB rats were exposed to several behavioral tests. LAB rats show less floating in the forced swim test, reduced risk assessment and more exploration in the modified hole board and open field compared with HAB rats [Liebsch et al., 1998a; Ohl et al., 2001; for review see Landgraf and Wigger, 2002]. Recently, we found that LAB rats show a higher level of intermale aggression compared with both HAB rats and unselected Wistar rats [Veenema et al., 2007]. Accordingly, the LAB rats are characterized by a 'proactive' coping style and the HAB rats by a 'reactive' coping style.

Extensive research has been conducted on the SAL and LAL mice and the HAB and LAB rats that generated reproducible results over many years, reflecting the reliability, consistency and robustness of the geno- and phenotypes of these selection lines. Cross-mating and/or embryo transfer and cross-fostering showed that the behavioral phenotype of the mouse [Sluyter et al., 1995, 1996b] and rat [Wigger et al., 2001] lines is genetically determined. The LAL mice and HAB rats have been proposed as animal models for human stress-related mood disorders such as anxiety and depression [Landgraf and Wigger, 2002; Veenema et al., 2004]. In contrast, the SAL mice and LAB rats are interesting candidates for analyzing neurobiological mechanisms involved in aggression and proactive stress coping. Because these lines are different species and are genetically bred for different selection criteria, direct comparisons between the lines are difficult. Considering this, finding similarities (but also dissimilarities) in neurobiological response patterns between SAL mice and LAB rats might improve our understanding of the causes of aggressive behavior.

First, different aspects of aggressive behavior in SAL mice and LAB rats will be discussed in more detail. To reveal neurobiological mechanisms underlying aggression in relation to stress coping, data on the following parameters will subsequently be discussed: (i) the hypothalamic-pituitary-adrenocortical (HPA) axis, (ii) neuronal activation patterns, (iii) the vasopressin (AVP) system, and (iv) the serotonin (5-HT) system.

Aggressive Behavior

Aggressive behavior is common in virtually all social animals and is considered functional when it is essential for the survival of the individual or species. Aggression is an efficient means of competition for food, territory, and exclusive mating and it serves to protect offspring from dangerous conspecifics. Aggression between two individuals of one species involves risks for both the recipient and perpetrator. As a result, the aggressive behavior between two males, for instance, is ritualized to avoid serious injuries and is clearly signaled in advance to offer the weakest one an opportunity to withdraw. When these species-specific rules are disregarded, male aggressive behavior can become abnormal or pathological. This is considered to be the case when, for example, a male attacks a female family member, or attack behavior is continued despite clear signs of submission, or when aggression is displayed outside of the proper context [Haller and Kruk, 2006].

In their home cage, male SAL mice are extremely aggressive; they attack a conspecific within seconds, and if not prevented by the experimenter, an opponent will be seriously injured and most likely killed [Sluyter et al., 2003]. The latter is likely due to the fact that SAL mice show a high percentage of abnormal attack targeting (28.8 $\pm$ 1.4%); that is, they show attacks at vulnerable body parts of the opponent such as the head, throat and belly [Haller et al., 2006]. SAL mice will also readily attack outside their home territory in either a neutral or foreign territory, and they attack females as well [Sluyter et al., 2002]. SAL mice seem to be less able to control their aggressive behavior and are easily provoked to escalated and violent aggression. Therefore, SAL mice are proposed as an animal model for antisocial behavior [Sluyter et al., 2003].

In male HAB and LAB rats, a significant inverse correlation was found between trait anxiety and aggression. LAB rats showed a shorter attack latency, more attacks and a higher level of intermale aggression when confronted with an unknown intruder male rat in their home-cage compared with both HAB rats and unselected Wistar rats [Veenema et al., 2007]. Preliminary analysis indicates that LAB rats show a high percentage of abnormal attack targeting [32.8 $\pm$ 8.5%, J. Halasz and A.H. Veenema, unpublished data]. Furthermore, even in a neutral [Veenema, unpublished data] or foreign territory [Frank et al., 2006], LAB rats display offensive behavior. Additionally, LAB rats make fewer non-aggressive social contacts with a male intruder [Veenema et al., 2007] and they show a lower level of social interactions with their cage mates [Henniger et al., 2000; Ohl et al., 2001] compared with HAB rats. These findings suggest that the display of high aggression in LAB rats is related to a general disturbance in social behavior.

To further analyze similarities in aggressive and stress response patterns in SAL mice and LAB rats, data on several neurobiological parameters are compared and discussed.

HPA Axis Responsiveness

One of the major stress systems is the hypothalamic-pituitary-adrenocortical (HPA) axis. Disturbances in HPA axis responses have frequently been reported in several human stress-related disorders [Plotsky et al., 1998; Mello Ade et al., 2003; de Kloet et al., 2005]. Additionally, HPA axis activity plays an important role in the regulation of aggressive behavior [Haller et al., 1998, 2001; Summers et al., 2005a]. Paradoxically, high as well as low HPA

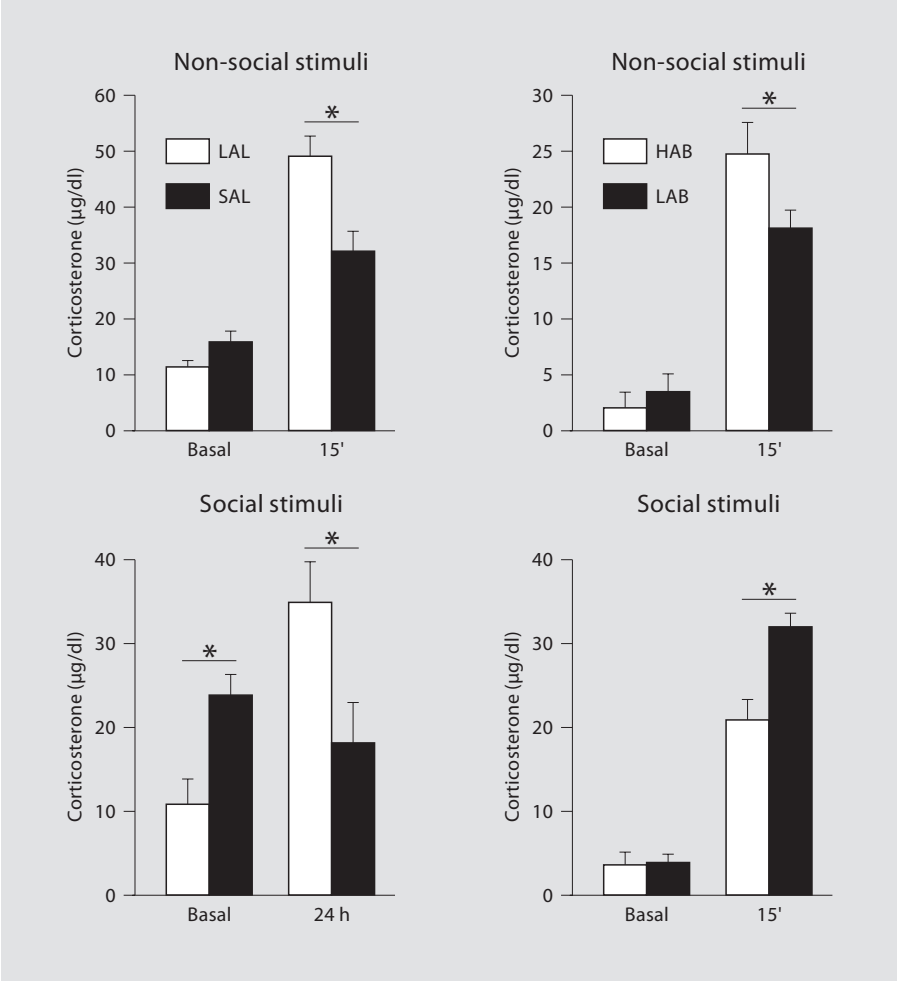

Fig. 1. SAL mice and LAB rats show a similar corticosterone response pattern to a non-social stimulus, whereas they show an opposite corticosterone response pattern to a social stimulus as compared with their line counterparts, the LAL mice and HAB rats, respectively. Non-social stimuli: SAL and LAL mice were decapitated under basal conditions or 15 min after a 5-min exposure to forced swimming and blood was collected for subsequent measurement of plasma corticosterone [data from Veenema et al., 2003b]; HAB and LAB rats were fitted with a jugular vein catheter 5 days prior the experiment and plasma corticosterone was measured before (basal) and 15 min after a 5-min exposure to an open arm of the elevated plus-maze [data from Landgraf et al., 1999]. Social stimuli: SAL and LAL mice were put in a novel cage (basal) or were exposed to sensory contact (except for physical contact) with an unknown SAL male and 24 h later blood was obtained by a tail cut for subsequent measurement of plasma corticosterone [Veenema et al., 2005a]. HAB and LAB rats were fitted with a jugular vein catheter 3 days before the rats were exposed as intruders to an unknown resident LAB male and after two fast attacks of the resident. A wire mesh was inserted between the rats allowing sensory contact and blood was collected before exposure to the resident and at 15 min of sensory contact [Frank et al., 2006]. Data are presented as means + SEM. * $p < 0.05$.

axis activity can be associated with excessive aggression. High HPA axis activity, often associated with a state of hyperarousal, is thought to underlie sudden outbursts of aggression, whereas chronically low HPA axis activity, often associated with a state of hypoarousal, might induce long-lasting changes in brain functions that promote violence [Haller et al., 2006]. Thus, the faulty regulation of HPA hormones might contribute to the escalation of violent behavior under stressful conditions [Kruk et al., 2004]. The exact mechanisms of these different forms of aggression are far from being understood. Therefore, it is of interest to study HPA axis responses to stressful stimuli in the high aggressive SAL mice and LAB rats.

SAL and LAL mice have been characterized for their neuroendocrine patterns under basal and stress conditions (see fig. 1) [for review, see Veenema et al., 2004]. SAL mice showed higher plasma corticosterone levels around the circadian peak and had lower plasma ACTH levels than LAL mice [Veenema et al., 2003b], suggesting a line difference in adrenocortical sensitivity to ACTH. No basal line differences were found for central markers of the HPA axis, i.e., corticotropin-releasing hormone (CRH) mRNA expression in the paraventricular nucleus (PVN) of the hypothalamus and hippocampal glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) mRNA expression [Veenema et al., 2003b]. Exposure to 5-min forced swimming resulted in a diminished corticosterone response in SAL compared with LAL mice [Veenema et al., 2003b]. Twenty-four hours after this stressor, SAL mice showed no changes in central HPA markers, whereas LAL mice showed increases in hippocampal MR mRNA and hypothalamic CRH mRNA [Veenema et al., 2003b]. When exposed to a psychosocial stressor (sensory contact), no changes in plasma corticosterone levels were found in SAL mice, but LAL mice showed long-lasting increases in plasma corticosterone

and a strong reduction in hippocampal MR mRNA expression [Veenema et al., 2003a, 2005a]. Thus, SAL mice seem to be resilient to stressful stimuli by showing an overall reduced responsiveness of the HPA system.

In HAB and LAB rats, investigation of the HPA axis to various stressful stimuli indicated profound differences in neuroendocrine stress coping (see fig. 1). Compared with HAB rats, LAB rats showed reduced plasma ACTH and corticosterone responses when exposed to non-social stressors, such as exposure to the open arm of the plus-maze [Landgraf et al., 1999; Salome et al., 2004; Neumann et al., 2005]. In contrast, when exposed to a larger male resident during social defeat, LAB intruders showed a higher HPA response than HAB rats [Frank et al., 2006]. Moreover, when exposed as a resident to a smaller intruder, LAB rats showed a high level of aggression which was accompanied by a higher HPA response compared with HAB intruders [Veenema et al., 2007]. No basal line differences were found for central markers of the HPA axis, that is, hippocampal GR and MR binding, GR and CRH1-receptor binding in the PVN, and GR binding and mRNA expression in the anterior pituitary [Keck et al., 2002; Wigger et al., 2004; Salome et al., 2006], except for lower CRH mRNA and CRH2-binding in the PVN of LAB compared with HAB rats [Wigger et al., 2004; Bosch et al., 2006]. Taken together, LAB males show a stressor-dependent HPA axis responsiveness to social conflict situations that seem to be highly stressful.

It is evident that both the SAL mice and the LAB rats show a diminished HPA response to non-social stressors. On the contrary, social stimuli induced a differential HPA response in SAL mice and LAB rats. This finding emphasizes the importance of using different types of stressors in order to reveal all facets of stress coping. In SAL mice, the overall reduced HPA responsiveness irrespective of the nature of the stressor might indicate a general state of hypoarousal. Hypoarousal might be causally involved in violence and aggressiveness seen in patients with personality disorders [Haller and Kruk, 2006], by diminishing emotional barriers that would normally inhibit such behaviors. In support of this, glucocorticoid hyporeactive rats showed violent forms of aggression [Haller et al., 2001]. Thus, the lower HPA reactivity seen in SAL mice might be associated with their prevalence to show excessive aggressive behavior. Clearly, further research is needed regarding a detailed analysis of neuroendocrine and autonomic responses of SAL mice during the display of aggression.

Unlike SAL mice, LAB rats show a high HPA response to social stimuli, indicating that LAB rats might perceive these stimuli as highly aversive and threatening. This is supported by the low level of non-aggressive social contacts of LAB rats with their cage mates [Henniger et al., 2000; Ohl et al., 2001] and during the resident-intruder test [Veenema et al., 2007]. It is unlikely that the higher HPA response in LAB rats reflects a higher rate of motor activity, as during forced swimming, for example, LAB rats are more active than HAB rats but show a reduced HPA response. An acute activation of the HPA axis indeed promotes aggressive behavior in rodents [Haller et al., 2000; Mikics et al., 2004]. In humans, high HPA responses have been associated with high levels of aggression in a number of psychiatric disorders, including mood disorders and intermittent explosive disorder [McBurnett et al., 2005; van Bokhoven et al., 2005]. To which extent the high HPA response to acute social stimuli contributes to the high level of aggression in LAB rats needs to be investigated. Interestingly, LAB rats show higher basal plasma norepinephrine and epinephrine levels [Salome et al., 2006] and a stronger increase in body temperature after defeat [Liebsch et al., 1998b] than HAB rats. These findings suggest a state of hyperarousal to certain stressful stimuli in LAB rats. It would be of interest to further characterize the role of HPA hormones and the sympathetic nervous system in the regulation of aggressive behavior in LAB rats.

As previously mentioned, both a low and a high level of HPA axis responsiveness can be associated with increased aggressiveness in humans. This paradoxical finding is also expressed in our two animal models, the SAL mice and LAB rats. This might further indicate that, despite the fact that both rodent lines show a proactive coping style, the high aggressiveness of SAL mice and LAB rats is induced by different neurobiological pathways.

Neuronal Circuits/Neuronal Activation

The regulation of aggression requires a complex circuit of interconnecting neuronal structures in the brain. In particular, amygdaloid, hypothalamic, septo-hippocampal, and cortical regions have been implicated in male aggression, as each of these regions plays a differential hierarchical role in the control over aggression. Impulsive aggression and violence could arise as a consequence of faulty emotion regulation [Davidson et al., 2000]. Indeed, patients with certain types of brain damage show a high prevalence of violence and aggressiveness [Kim, 2002; Kanner, 2004; Sachs, 2006], indicating that excessive aggression can occur when certain brain cir-

Table 1. Neuronal activation (indicated by the number of c-Fos-positive neurons) of specific brain regions of resident SAL mice and LAB rats after exposure to a resident-intruder test

	SAL mice	LAB rats
Frontal cortex	higher activation	no line difference
Lateral septum	**reduced activation**	**reduced activation**
BNST	higher activation	no line difference
PVN	no line difference	higher activation
CeA	**higher activation**	**higher activation**
MeA	no line difference	higher activation
AH/HAA	no line difference	higher activation
PAG ventrolateral	higher activation	not determined
PAG dorsolateral	reduced activation	not determined

A change in activation in SAL mice or LAB rats is in comparison with their line counterparts, the LAL mice and the HAB rats, respectively. Neuronal activation of the lateral septum and the CeA (marked in bold) was found to show a similar direction of change in SAL mice and LAB rats as compared to their line counterparts.

AH = Anterior hypothalamus; BNST = bed nucleus of the stria terminalis; CeA = central amygdala; HAA = hypothalamic attack area; MeA = medial amygdala; PAG = periaqueductal grey; PVN = paraventricular nucleus of the hypothalamus. Data of the SAL and LAL mice are based on Haller et al. [2006], data of the HAB and LAB rats are based on Veenema et al. [2007] and Beiderbeck et al. [2007].

cuits are not accurately functioning. In animal research, the activity of neuronal circuits involved in aggression and other stress responses is generally measured by the protein expression of the immediate early gene *c-fos* [Halasz et al., 2002a; Martinez et al., 2002]. Here, we compare and discuss neuronal activation patterns in SAL mice and LAB rats exposed to aggressive encounters.

In SAL and LAL mice, neuronal activation was studied 1 h after a 5-min exposure to a resident-intruder test (table 1). In this test, SAL and LAL mice are exposed as residents to a novel intruder male mouse in their home-cage. In the highly aggressive SAL mice, increased neuronal activation was found in the frontal cortex, the bed nucleus of the stria terminalis (BNST), the central amygdala, and the ventrolateral parts of the periaqueductal grey compared with LAL mice [Haller et al., 2006]. In contrast to LAL mice, SAL mice showed a lack of neuronal activation in the lateral septum and the dorsolateral parts of the periaqueductal grey [Haller et al., 2006]. No line difference between LAL and SAL mice was found for neuronal activation in the PVN, medial amygdala or anterior hypothalamus.

In HAB and LAB rats, neuronal activation was studied 2 h after exposure to a 10-min resident-intruder test (table 1). In high-aggression LAB rats, more neuronal activation was found in the PVN, the central amygdala, the medial amygdala and the hypothalamic attack area compared with HAB rats [Veenema et al., 2007]. In the lateral septum, reduced activation was found in LAB compared with HAB rats [Beiderbeck et al., 2007]. No line difference between HAB and LAB rats was found for neuronal activation in the frontal cortex or BNST.

Exposure to the resident-intruder test induced a high neuronal activation in the central amygdala of both SAL mice and LAB rats. Central amygdala activation is seen in violent forms of aggression displayed by glucocorticoid deficient rats [Halasz et al., 2002a] or elicited by electrical stimulation of the hypothalamus [Halasz et al., 2002b]. Moreover, a strong activation of the central amygdala was also reported in response to the display of maternal and defensive aggression [Martinez et al., 1998; Hasen and Gammie, 2005]. These types of aggression are all characterized by violent attacks aimed at vulnerable body parts of the opponent. Activation of the central amygdala, known to be involved in fear responses [Davis and Shi, 1999], might play a major role in the expression of violent attacks [Haller et al., 2006]. Therefore, high central amygdala activation during offensive aggression in SAL mice and LAB rats might be associated with their propensity to show violent attacks. In LAB rats, it would be of interest to examine whether high central amygdalar activation is linked to their avoidance of and fear for social stimuli.

In SAL mice and LAB rats, exposure to the resident-intruder test was associated with a decrease in neuronal activation of the lateral septum. This is in contrast with other studies showing a positive relationship between the display of aggression and lateral septum activation [Halasz et al., 2002a; Ricci et al., 2007]. Moreover, a pharmacologically induced decrease in aggression was associated with a decrease in neuronal activation of the lateral septum [Trainor et al., 2006]. However, the lateral septum plays a critical role in the modulation of a wide range of emotions, including fear and anxiety [Sheehan et al., 2004]. Electrical stimulation of the lateral septum reduces anxiety, whereas lesioning the lateral septum can induce fear and defensive aggressive responses [Sheehan et al., 2004]. It has been suggested that attacks are promoted when modulatory brain regions, such as the lateral septum, are suppressed [Siegel et al., 1999]. Thus, the reduced activation of the lateral septum in resident SAL mice and LAB rats might enhance attack behavior.

Taken together, increased central amygdala activation and reduced lateral septum activation seem to be indicators of altered emotional regulation in SAL mice and LAB rats contributing to their high levels of aggressive behavior during social conflict situations. It would be of interest to further investigate the role of these two brain regions in the regulation of aggression and the involvement of local neurotransmitter systems such as the AVP and 5-HT systems.

The AVP System

The neuropeptide AVP, released within distinct brain regions [Landgraf and Neumann, 2004], plays an important role in the regulation of various emotional behaviors including aggression [Ferris, 1992]. In particular, the extra-hypothalamic AVP pathway originating in the BNST and medial amygdala and projecting to the lateral septum has been implicated in male aggression [de Vries and Miller, 1998]. For example, a denser AVP staining in the BNST and more AVP receptors in the lateral septum were found in the more aggressive male California mice compared with the less aggressive white-footed mice of the *Peromyscus* species [Bester-Meredith et al., 1999]. Furthermore, injection of AVP into the cerebral ventricles activates aggressive behavior in voles [Winslow et al., 1993]. In hamsters, microinjection of AVP within the ventrolateral hypothalamus, anterior hypothalamus, BNST or lateral septum facilitates offensive aggression [Irvin et al., 1990; Delville et al., 1996; Ferris et al., 1997]. Moreover, in patients with personality disorders, AVP concentrations in cerebral spinal fluid were positively correlated with a life history of aggressive behavior [Coccaro et al., 1998]. Recently, we could demonstrate that Wistar rats, subjected to maternal separation, showed an increase in intermale aggression, which was associated with a higher AVP-immunoreactivity in the PVN and the lateral hypothalamus [Veenema et al., 2006]. These findings support the suggestion that brain AVP promotes male aggression. However, results from both SAL mice and LAB rats conflict with this view.

In SAL mice, AVP projections from the BNST to the lateral septum were less dense than in LAL mice [Compaan et al., 1993]. Moreover, AVP-immunoreactive neuronal density in the BNST was lower in SAL compared with LAL mice [Compaan et al., 1993]. These differences in the organization of the forebrain AVP network might be linked to the line difference in levels of aggression, but direct experimental evidence is lacking so far.

In HAB rats, a single nucleotide polymorphism in the promoter region of the AVP gene [Murgatroyd et al., 2004] was recently found to underlie their higher AVP expression and release within the PVN which was causally linked to their high level of anxiety compared with LAB rats [Keck et al., 2002; Wigger et al., 2004]. These findings provided a basis to study line differences in the AVP system in brain regions implicated in aggression. Therefore, we applied intracerebral microdialysis to monitor the in vivo AVP release within the lateral septum during the display of aggression in HAB and LAB rats. Basal AVP release within the lateral septum was not different between the two lines [Beiderbeck et al., 2007]. However, the highly aggressive LAB rats showed a significant decrease in septal AVP release during exposure to a resident-intruder test [Beiderbeck et al., 2007]. This was associated with a reduced neuronal activation of the lateral septum as mentioned earlier, suggesting an overall decreased responsiveness of the lateral septum in LAB rats during the display of aggression.

These findings from independent studies in SAL mice and LAB rats indicate that a reduced septal AVP activity might also be linked to high levels of aggression. Although this seems to be in contrast with several studies cited above showing a positive correlation between brain AVP and aggression, there are a few studies suggesting the opposite. For example, high levels of offensive aggression in male wild type rats was associated with low AVP immunoreactive density and low AVP levels in the lateral septum [Everts et al., 1997]. Moreover, the more aggressive prairie voles showed fewer AVP-immunoreactive cells in the BNST and medial amygdala, and fewer AVP receptors in the lateral septum compared to the less aggressive meadow voles [Insel et al., 1994; Wang, 1995; Young et al., 1997]. Thus, data so far are inconclusive about the precise role of brain AVP in male aggression. This might be due to the complex organization of the AVP system which largely varies between and within species [Ferris et al., 1995; Wang et al., 1998]. For instance, the lateral septum is almost devoid of AVP immunoreactive fibers in male golden hamsters [Ferris and Delville, 1994], whereas a dense network of AVP fibers can be found in male mice and rats [Koolhaas et al., 1998]. This large variation in the AVP system might underlie species-specific regulation of social behaviors, including aggression. Furthermore, several studies used immunocytochemistry to detect AVP protein levels, but this technique does not provide information about the dynamics of local in vivo secretory release of AVP. Depending on the experimental design, low as well as high AVP staining might

be interpreted as an increase in (or even inhibition of) AVP release. Thus, other techniques are needed to reveal more accurately the role of brain AVP in aggression. Our data obtained with intracerebral microdialysis in LAB rats might be the first study that truly demonstrates a significant change in the physiological activity of the AVP system within the septum during the display of aggression. Further detailed analysis about the involvement of endogenous AVP in different brain regions in the regulation of aggression is warranted.

The 5-HT System

5-HT is mainly produced by a small number of cells in brain stem raphe nuclei, which send 5-HT projections to numerous brain regions. 5-HT influences a wide range of emotions and behaviors. The prevailing view has been that 5-HT exerts an inhibitory control over aggression [Linnoila and Virkkunen, 1992; Kavoussi et al., 1997]. In humans, excessive aggression and impulsive violent behaviors are associated with low cerebrospinal fluid levels of the 5-HT metabolite 5-hydroxyindolacetic acid [Berman et al., 1997]. However, recent findings in animal research challenge this 5-HT deficiency hypothesis of aggression, in which 5-HT is positively associated with the display of aggression [Olivier, 2004; de Boer and Koolhaas, 2005]. These opposing views might demonstrate important differences in 5-HT functioning in abnormal or pathological forms of aggression compared with normal and adaptive levels of aggression. Likewise, there might be essential differences regarding the role of the 5-HT system in trait-like and state-like aggression. Trait-like (abnormal) aggression can be associated or induced by chronically reduced 5-HT activity [Miczek et al., 2002], whereas state-like aggression is characterized by increased 5-HT activity [van der Vegt et al., 2003a, b; Summers et al., 2005b]. Additionally, contradictory findings could be explained by the complex involvement of two key players of the 5-HT system in aggression: the 5-HT1A and 5-HT1B receptors. These receptors are located postsynaptically, where they have a largely inhibitory effect on target neurons, as well as presynaptically, where they function as autoreceptors and inhibit brain 5-HT release. Accordingly, systemically administered 5-HT1A or 5-HT1B receptor agonists might change the level of aggression, but it is not clear whether this is due to an activation (postsynaptic effect) or an inhibition (presynaptic effect) of the 5-HT system. Although the involvement of the 5-HT system in aggression is indisputable, its precise role is still far from being clear. Thus, characterization of the 5-HT system in highly aggressive rodents such as the SAL mice and LAB rats might be of great relevance.

It was indeed found that SAL and LAL mice differ in certain parameters of the brain 5-HT system. SAL mice show higher hippocampal postsynaptic 5-HT1A receptor expression levels and binding capacity [Korte et al., 1996; Veenema et al., 2005b], and this is accompanied by a higher 5-HT responsiveness [van der Vegt et al., 2001; van Riel et al., 2002]. Although no line difference was found between LAL and SAL mice for presynaptic 5-HT1A autoreceptor expression levels in the dorsal raphe [Veenema et al., 2005b], a higher 5-HT1A autoreceptor sensitivity was found in SAL mice [Caramaschi et al., 2007]. Under basal conditions, SAL mice have a higher 5-HT turnover in the striatum and amygdala, whereas exposure to an acute stressor (forced swimming) induced a higher 5-HT turnover in SAL mice in several brain regions, including the septum [Veenema et al., 2005b]. Systemic application of the full 5-HT1A receptor agonist 8-OH-DPAT prevented this stress-induced increase in 5-HT turnover only in SAL mice [Veenema et al., 2005b], suggesting a predominant activation of 5-HT1A autoreceptors by 8-OH-DPAT. These line differences in 5-HT1A receptor properties and 5-HT metabolism might play a role in line differences in stress coping and male aggression. Considering the latter, the preferential somatodendritic 5-HT1A autoreceptor agonist S-15535 reduced aggressive behavior considerably in SAL males [S.F. de Boer, unpublished data]. Taken together, SAL mice showed a higher 5-HT activity in specific brain regions, particularly in response to stress, and inhibition of brain 5-HT release reduced the level of aggression displayed by SAL mice.

HAB and LAB rats are also characterized by differences in their 5-HT system. LAB rats show higher hippocampal 5-HT1A receptor mRNA levels and a lower expression of 5-HT transporter binding sites [Keck et al., 2005]. Basal hippocampal 5-HT release was not different between HAB and LAB rats, whereas exposure to an acute stressor induced a small rise in intrahippocampal 5-HT release in LAB rats only [Keck et al., 2005]. Chronic treatment with a 5-HT reuptake inhibitor paroxetine had no effect on this stress-induced rise in hippocampal 5-HT in LAB rats but it did elicit a rise in HAB rats [Keck et al., 2005]. Following exposure to an acute stressor, LAB rats showed a lower increase in 5-HT release in the PVN [Umriukhin et al., 2002], but a higher 5-HT turnover in the lateral septum and amygdala [Salome et al., 2006] compared with HAB rats. These findings might indicate higher 5-HT neurotransmission in most brain regions in LAB rats.

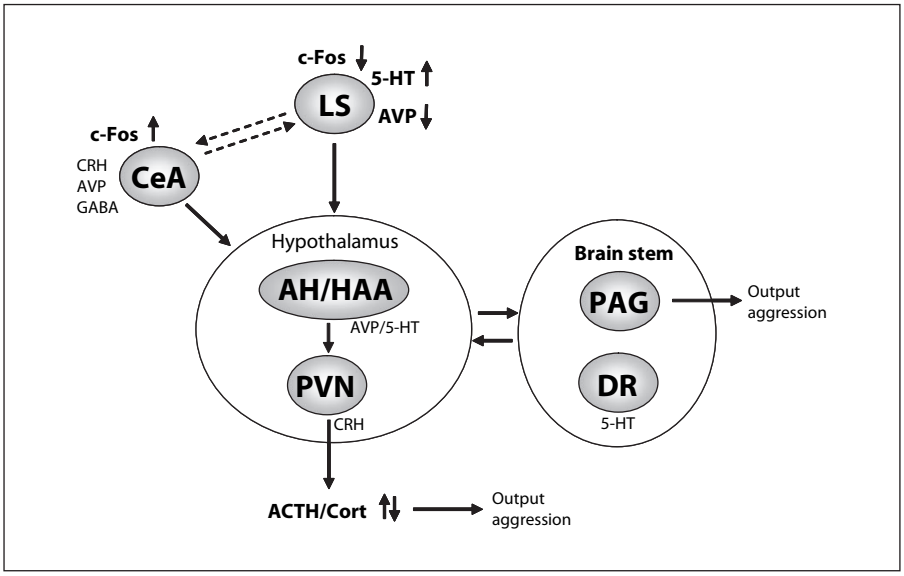

Fig. 2. Simplified and hypothetical model of the neuronal circuitry of aggression based on findings with SAL mice and LAB rats. The anterior hypothalamus/hypothalamic attack area (AH/HAA) and the periaqueductal grey (PAG) are two important brain regions involved in attack control. The AH/HAA receives direct input from the central amygdala (CeA) and the lateral septum (LS). High activation of the CeA (as indicated by enhanced c-Fos expression in SAL mice and LAB rats after an aggressive encounter) leads to activation of the AH/HAA. Reduced activation of the lateral septum (as indicated by increased 5-HT activity, decreased AVP activity, and reduced c-Fos neuronal activation in SAL mice and LAB rats) results in reduced inhibition of the AH/HAA. The net outcome is enhanced AH/HAA activity, leading to enhanced activation of parts of the PAG and resulting in enhanced attack behavior. In addition, the paraventricular nucleus (PVN) receives input from several hypothalamic regions including the AH/HAA, limbic brain regions such as the CeA and the LS, and brain stem regions such as the PAG and dorsal raphe (DR). Upon activation of the PVN, corticotropin-releasing hormone (CRH) will enhance pituitary-adrenocortical activity by inducing the release of ACTH and corticosterone. Increased as well as reduced activation of this hypothalamus-pituitary-adrenocortical (HPA) axis results in enhanced attack behavior via yet unknown central pathways.

Thus, SAL mice and LAB rats show indications of higher 5-HT neurotransmission compared with their line counterparts, which might be related to their proactive coping style. Indeed, it is well known that 5-HT facilitates behavioral arousal and motor activity [Jacobs and Fornal, 1999], which is obviously necessary for the initiation and execution of aggressive behavior [Olivier and van Oorschot, 2005]. Nevertheless, as outlined above, abnormal aspects of aggression seem to be linked to low (trait-like) 5-HT activity. Although the SAL mice and LAB rats might show signs of excessive aggression, in contrast the present findings suggest a positive relationship between 5-HT activity and aggression. Future research should validate this by measuring local 5-HT release patterns during the display of aggression. In this context, the lateral septum and the amygdala are of particular interest, as here a higher 5-HT turnover is seen in SAL mice and LAB rats, and these two regions showed an opposing neuronal activation pattern in response to a resident-intruder test in SAL mice and LAB rats.

Conclusions

We are still far from understanding the neurobiological mechanisms underlying complex behaviors such as male aggression. As the expression of aggression involves numerous biochemical pathways, multidimensional studies using detailed analyses of behavior in combination with analyses of molecular, cellular, and systematic parameters are needed. Here, we discussed the involvement of the HPA, AVP and 5-HT systems and neuronal activation patterns in high aggressive SAL mice and LAB rats (see table 2 and fig. 2). A difference between SAL mice and LAB rats was found for HPA axis responsiveness to social stimuli, whereas similarities were found for parameters of the AVP and 5-HT systems and for neuronal activation patterns. These findings reveal that a certain balance between these relevant neurobiological mechanisms is required for the regulation of adaptive aggressive behavior, whereas a very low or a very high activity in one or more systems might underlie abnormal

Table 2. Overview of parameters of the HPA, AVP and 5-HT systems in male SAL mice and LAB rats as compared with their line counterparts, the LAL mice and HAB rats, respectively. See text for details

	SAL mice	LAB rats
HPA axis responses		
Non-social stressors	reduced HPA activation	reduced HPA activation
Social stressors	reduced HPA activation	higher HPA activation
AVP in LS	reduced AVP fibers	reduced AVP release during aggression
5-HT system		
5-HT1A receptor	higher in hippocampus	higher in hippocampus
5-HT turnover in LS	higher	higher
5-HT turnover in CeA	higher	higher

CeA = Central amygdala; LS = lateral septum.

behavioral responses. Although further, more detailed research is necessary, comparative studies in different selection lines, such as the ones presented here, provide valuable information about neurobiological mechanisms underlying particular behavioral patterns including male aggression. As aggressive disorders cause major public health and social problems, preclinical research seems to be essential for future prevention and management of abnormal aggression levels in humans.

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