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European Journal of Pharmacology 526 (2005) 89–100
www.elsevier.com/locate/ejphar

Review

Mechanisms differentiating normal from abnormal aggression: Glucocorticoids and serotonin

Jozsef Haller *, Éva Mikics, József Halász, Máthé Tóth

Institute of Experimental Medicine, Hungarian Academy of Science, 1450 Budapest, P.O. Box 67, Hungary

Accepted 23 September 2005
Available online 8 November 2005

Abstract

Psychopathology-associated human aggression types are induced by a variety of conditions, are behaviorally variable, and show a differential pharmacological responsiveness. Thus, there are several types of abnormal human aggression. This diversity was not reflected by conventional laboratory approaches that focused on the quantitative aspects of aggressive behavior. Recently, several laboratory models of abnormal aggression were proposed, which mainly model hyperarousal-driven aggressiveness (characteristic to intermittent explosive disorder, post-traumatic stress disorder, depression, chronic burnout, etc.) and hypoarousal-driven aggressiveness (characteristic mainly to antisocial personality disorder and its childhood antecedent conduct disorder). Findings obtained with these models suggest that hyperarousal-driven aggressiveness has at its roots an excessive acute glucocorticoid stress response (and probably an exaggerated response of other stress-related systems), whereas chronic hypoarousal-associated aggressiveness is due to glucocorticoid deficits that affect brain function on the long term. In hypoarousal-driven aggressiveness, serotonergic neurotransmission appears to lose its impact on aggression (which it has in normal aggression), certain prefrontal neurons are weakly activated, whereas the central amygdala (no, or weakly involved in the control of normal aggression) acquires important roles. We suggest that the specific study of abnormal aspects of aggressive behavior would lead to important developments in understanding the specific mechanisms underlying different forms of aggression, and may ultimately lead to the development of better treatment approaches.

Keywords: Aggression; Abnormal; Glucocorticoid

Contents

* Corresponding author. Tel.: +36 12109406; fax: +36 12109951.
E-mail address: haller@koki.hu (J. Haller).

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doi:10.1016/j.ejphar.2005.09.064

1. Introduction: pathology and aggression

Aggression per se cannot be considered abnormal. This behavior is among the most efficient means of competition, which ensures individual survival and genetic success when resources are limited. As such, it is common in virtually all species that have a neural system and physical constitution suitable for performing it. Under certain conditions, human aggressive behavior can remain legitimate even in its crude physical form, and even more so when these give way to more advanced exercises of power. The legitimacy of many such behaviors has never been questioned; moreover, one can hypothesize that a totally peaceful society would become exceedingly vulnerable to newly arising aggressive attempts.

Although normal, aggression is limited by rules. In humans, rules are formalized as laws, but rules exist at the moral and biological levels as well. Serious, frequent, and harmful violation of such rules (be those judicial, moral or biological) endangers social functioning, which is abnormal for a species as highly social as humans. The general criteria for classifying a behavior abnormal are inappropriateness, frequent or prolonged expression, and burden. Many forms of aggressiveness and violence certainly fulfill these criteria. The behavioral response to challenges (e.g., an aggressive outburst) is in some cases disproportionate compared with the challenge, is excessively frequent, and results in suffering not only for the victim, but also for the perpetrator. For example, antisocial personality disorder–frequently associated with violence–shortens life expectancy (Rydelius, 1988; Martin et al., 1985). Thus, there are cases when a functional behavioral response (e.g., aggressiveness) becomes inappropriate. In this respect, the case of aggressive behavior is not very different from that of anxiety and depression. Both these behaviors are adaptive under certain conditions; e.g., anxiety inhibits dangerous activities, whereas depression serves survival by reducing activity under extreme pressure. Anxiety and depression become abnormal only when they occur inappropriately. Similarly, aggression is a means of competition, but becomes abnormal when expressed out of context or is exceedingly intense. The abnormality of certain forms of aggressiveness is also supported by the fact that they are usually embedded in a wider array of psychological dysfunctions, and parallel serious psychological disorders of various kinds (see below).

Thus, aggression is a means of competition, which is normal per se, but becomes abnormal when rules limiting it are seriously, and frequently broken. Human and laboratory findings suggest that aggressive behavior can become abnormal in several ways, and different forms of aggression have a specific physiological and neural background. In the following we will outline the main types of abnormal human aggression and their physiological correlates, will present novel laboratory models of abnormal aggression, and will summarize findings regarding their specific endocrine and neural control. We suggest that research into the mechanisms underlying different forms of abnormal aggression would reveal important aspects that ultimately may lead to the design of novel and more appropriate treatment approaches.

2. The phenomenology of abnormal aggression

2.1. Abnormal aggression in humans

2.1.1. Psychopathology and aggressiveness

In clinical research, aggressiveness is rarely tackled as an independent biological problem. The abnormality of aggressiveness is usually addressed in terms of psychopathology, and aggressiveness is viewed as one of the symptoms that may or may not occur in a particular disorder. We will conform to this general consensus, and will address the issue from a psychopathologic point of view.

There are a relatively large number of psychopathologies consistently associated with aggressive behavior. Even being admitted to a psychiatric ward was shown to increase the odds ratio of violence to 3–5 (i.e., these people are 3–5 times more likely to commit acts of violence than the general population; Hodgins, 1998). Disorders consistently associated with aggressiveness include Alzheimer's's disease, antisocial personality disorder, attention deficit/hyperactivity disorder, conduct disorder, depression, epilepsy, frontal brain injury, mental retardation, schizophrenia, schyzotypal disorder, and substance abuse (including alcohol, cocaine, amphetamine, metamphetamine, and phencyclidine abuse). The prevalence of these psychopathologies is typically around 2% (taken separately) and their association with aggressiveness is variable. In some disorders, the impact of aggressiveness is minimal at the level of the society, whereas in other disorders aggressiveness is a large-scale social problem. In antisocial personality disorder, the odds ratio of aggressive/violent behavior are around 7.2 : 12.1 (males:females; general population = 1), the odds ratio of family violence is 48, whereas the odds ratio of homicide is around 11 (Ekselius et al., 2001; Moran, 1999; Eronen et al., 1998). In schizophrenia, the odds ratio of homicide rises to 7 if the

disorder is not associated with alcoholism, and rises to 17 otherwise (i.e., alcoholic schizophrenics are 17 times more likely to commit homicide than psychologically healthy individuals) (Link et al., 1998; Pontius, 1984; Eronen et al., 1998; Brieden et al., 2002). The vast majority of posttraumatic stress disordered patients are aggressive (Beckham et al., 2000). The size of the problem is convincingly illustrated by studies investigating prison populations. Among convicted violent offenders, the majority showed substance abuse (63.75% alcoholism, and 60% illicit drug consumption; Boles and Miotto, 2003), 40%–60% showed antisocial personality disorder (Moran, 1999), 3.7%:4.0% (males:females) showed psychosis, 47%:2 1% (males:females) showed schizophrenia (Fazel and Danesh, 2002), whereas 32% showed post- traumatic stress disorder (Steiner et al., 1997) (naturally, many of these disorders are co-morbid). These figures are considerably above the prevalence of the respective disorders in the general population. An interesting study addressed the psychological functioning of a death row sample (Freedmann and Hemenway, 2000). Among these people convicted for premeditated murder, the prevalence of post-traumatic stress disorder was 86%, that of severe depression 80%, polysubstance abuse was shown by 80%, 74% had brain injury, 68% showed brain impairment, whereas 56% showed psychosis. A little more than one tenth of the sample (12%) showed all the 6 disorders in parallel, 44% showed 5 disorders, 25% showed 4 disorders, whereas 19% showed 3 disorders. No patient showed less than 3 disorders at a time. Considering that all these people suffered in addition from multiple psychosocial (Axis-IV) problems during their lives, it does not appear exaggerated to state that they were severely impaired in psychological terms. Based on such data, one is prone to hypothesize that all those who commit serious acts of violence are psychologically disordered, and most show multiple disorders. Therefore, tackling the problem of aggression from the point of view of psychopathology appears justified.

2.1.2. Types of abnormal human aggressiveness

Human data point to the existence of several forms of abnormal human aggressiveness. These forms differ in all three: conditions leading to their development, their physiological and behavioral correlates and pharmacological responsiveness. These differences appear highly relevant for their management. In principle, abnormal human aggression (violence) appears to develop under three major circumstances: (i) when the brain is damaged accidentally, during neurodegenerative disorders, or due to several other conditions (e.g. drug abuse), (ii) in states associated with hyperarousal, and (iii) in chronic states of hypoarousal.

Brain damages of various kind (frontal and temporal brain injury, epilepsy-related and Alzheimer's's disease-related cell death, etc) lead to aggressiveness and violence (Hawkins and Trobst, 2000; Van Elst et al., 2000; Kanemoto et al., 1999; Paveza et al., 1992; Nagaratnam et al., 1998; Lai et al., 2003; Victoroff et al., 1996). Noteworthy, aggressive behavior appears to be linked to specific patterns of neuronal damage or degeneration in these psychopathologies. In general, aggression is relatively rare in epilepsy patients but their likelihood increases considerably in temporal lobe epilepsy (Van Elst et al., 2000; Kanemoto et al., 1999). Similarly, Alzheimer's's disease consistently leads to aggressiveness especially when serotonin 5-HT_{1A} receptor binding is reduced in the temporal cortex, and when the substantia nigra pars compacta is not damaged (Lai et al., 2003; Victoroff et al., 1996). It is also clear that the accidental damage of frontal and temporal cortices but not of other areas lead to aggression. The specific association of aggressiveness with certain types of brain damage suggests that aggressiveness develops when brain mechanisms directly or indirectly linked to aggression are affected. Aggression associated with certain clinical disorders (e.g. schizophrenia, attention deficit/hyperactivity disorder, and drug abuse) might be classified into this category, although direct brain damage cannot be noticed. In these cases, functional alterations in brain function probably underlay aggressiveness.

There are several disorders in which increased arousal plays an important role in aggressiveness. Sudden outbursts of aggression occur in both intermittent explosive disorder (where these constitute the essence of the disorder) and depression (where these outbursts are called anger attacks) (Kavoussi et al., 1997; Biondi et al., 2005; Eronen et al., 1998; Fava et al., 2000; Olvera, 2002; van Praag, 2001). In both cases, aggressive outbursts are accompanied by excessive autonomic arousal and affective reactions (e.g., anger). Hyperarousal also plays a role in irritable aggression that characterizes chronic burnout and post-traumatic stress disorder (Melamed et al., 1999; Southwick et al., 1999; Elzinga et al., 2003; Bremner et al., 2003a,b).

Hypoarousal-driven aggressiveness occurs especially in violent people showing antisocial personality disorder or its childhood antecedent conduct disorder. Aggressiveness in these disorders is associated with low plasma glucocorticoid levels (McBurnett et al., 2000; Pajer et al., 2001; van Goozen et al., 1998; Vanyukov et al., 1993; Kariyawasam et al., 2002; Virkkunen, 1985; Dolan et al., 2001), reduced adrenaline stress reactions, as well as reduced autonomic and skin conductance responsiveness to stress (Raine, 1996a,b; Herpertz et al., 2001; Brennan et al., 1997; Woodman and Hinton, 1978). Basal heart rate and skin conductance are also reduced. Part of these findings lead to the emergence of the "hypoarousal theory" of violence (Raine, 1996a,b). Hypoarousal was deemed to lead to violence by removing the emotional barriers that limit such behaviors.

Importantly for the present study, aggression shown during various psychopathologies takes different forms: antisocial personality disordered patients frequently show instrumental aggression, depressed patients experience sudden spells of anger, whereas post-traumatic stress disorder is characterized by hostility, weapon collection, etc. (Woodworth and Porter, 2002; Fava, 1998; Beckham et al., 2000). There are no data on weapon collection and composed instrumental aggression in depression or intermittent explosive disorder; similarly, anger outbursts are lesser problems in antisocial personality disorder than "cool blooded" violence. Thus, aggressiveness associated with different psychopathologies show large behavioral differences.

The pharmacological responsiveness of various forms of abnormal aggression is also specific; e.g. aggressiveness expressed by attention deficit/hyperactivity disordered patients is efficiently ameliorated by psychostimulants (Casat et al., 1995; Connor et al., 2000; Gadow et al., 1990), which do not reduce aggressiveness in other disorders (e.g. conduct disorder, depression, schizophrenia, brain injury; Fleminger et al., 2003). In addition, agents that ameliorate other types of aggressiveness (MAOIs, antipsychotics, desipramine, buspirone, benzodiazepines, carbamazepine, lithium) are without effect in this disorder (Popper, 2000). The anti-aggressive effects of pharmacological interventions appear disorder-specific in other disorders as well. Selective serotonin reuptake inhibitors, although efficient against aggressiveness in a variety of disorders, were shown to have a low efficacy in personality disorders (Kavoussi and Coccaro, 1998; we will discuss this issue in more detail below). Benzodiazepines, efficient against aggressiveness in dementia, and acute aggressive episodes in a variety of disorders (Herrmann, 2001; Dorevitch et al., 1999; Buckley, 1999), lead to disinhibition in agitated and irritable elderly (Fava, 1997), and increase behavioral dyscontrol in borderline disorder and schizotypal disorder (Cowdry and Gardner, 1988; Hori, 1998).

2.1.3. Summary

There are a large number of human psychopathologies that are consistently associated with aggressiveness and violence. There appear to be at least three different types of conditions that lead to abnormal aggression: brain damage, hyperarousal, and hypoarousal. Aggressive behaviors shown during various disorders appear different in behavioral terms, and show a differential pharmacological responsiveness. Thus, aggression cannot only be pathological in humans, but the existence of several types of abnormal aggression can be assumed.

2.2. Abnormal aggression in the laboratory

2.2.1. Conventional ways of studying aggression in the laboratory

Compared with the multitude of forms that human aggression can take, laboratory models of aggression–especially the conventional models–appear rather poor and unilateral. The ultimate measures of aggressiveness are quantitative in nature: aggression is usually characterized by the time spent with, and the frequency of, agonistic behaviors. This state of affairs holds true even for the cases when aggression-related psychopathologies are modeled. For example, aggressiveness was studied in animals submitted to experimental brain lesions (de Bruin et al., 1983; Albert and Walsh, 1984), in various models of Alzheimer's's disease (Dewachter et al., 2001; Hortnagl et al., 1989), epilepsy (Cook, 1999; Desjardins and Persinger, 1995; Bolivar et al., 2002), post-traumatic stress disorder (Pynoos et al., 1996), depression (Tannenbaum et al., 2002; Mineur et al., 2003), etc. By and large, aggressiveness was affected in these models in a way consistent with the respective human disorders, although inconsistent findings were also reported. The major drawback of these studies was that no measures of abnormal aggression were employed, and aggressiveness was evaluated in quantitative terms only. There are several reasons why such quantitative approaches are inappropriate for evaluating the abnormal aspect of aggressive behavior. The intensity of aggressive behavior shows a bimodal distribution (de Boer et al., 2003), and individual variations in aggressiveness correlate with coping styles that have differential adaptive values in different environments (Koolhaas et al., 1999). The aggressiveness of animals shows ultradian, diurnal and seasonal variations (Caldwell et al., 1984; Haller et al., 2000; Lincoln and Davidson, 1977). It is difficult to assume that coping styles, or natural oscillations in aggressiveness reflect oscillations in abnormality. The most solid argument, however, against the quantitative approach is that it oversimplifies the issue, and loses the diversity seen in human aggression. After all, the abnormality of human aggression cannot be reduced to quantitative measures. Abnormally aggressive people are not abnormal because they fight more when anybody would fight, but because they fight when virtually no psychologically healthy person would do so.

2.2.2. Novel approaches

The interest in abnormal aggression is relatively new in animal research. Recently, three ways of studying and identifying abnormal forms of attack were proposed: (i) studying escalated levels of aggression induced by "frustration" (e.g. by omission of scheduled reward) or "instigation" (by pre-exposure to a potential opponent). Thus, rats are hyperaroused before the aggressive encounter in this model, which allows the study of aggressive behaviors that exceed species-typical levels (de Almeida and Miczek, 2002; Miczek et al., 2002); (ii) identifying impulsive behavioral strategies, and altered sequential structures of aggressive behavior, which would allow the study of aggressive acts that lost their function in social communication (de Boer et al., 2003); and (iii) following the development of abnormal attack targeting, i.e. the ratio of attacks aimed at vulnerable targets (e.g., head, throat and belly; Haller et al., 2001). We used this latter approach to characterize the aggressiveness of rats with experimentally induced hypoarousal. Pharmacological and functional neuroanatomical studies on these models showed that the neural control of abnormal forms of aggression is specific and different from the control of normal aggression (de Almeida and Miczek, 2002; Miczek et al., 2002, 2003; Haller et al., 2005; Halasz et al., 2002). The use of such models promises the obtaining of insights into brain mechanisms that could not be obtained by more conventional approaches, which model abnormal aspects considerably less closely.

2.2.3. Summary

Conventional laboratory studies on aggression neglected for long the abnormal aspect of aggressive behavior. By focusing on quantitative aspects, laboratory research failed to reproduce the multitude of forms that psychopathology-driven human aggression can take. Novel approaches were developed to address abnormal forms of aggression, especially those related to hyper- and hypoarousal. Such approaches model the human condition more closely, and offer the chance of understanding

brain mechanisms that differentiate normal and abnormal forms of aggression, as well as different forms of abnormal aggression.

3. Glucocorticoids in different forms of abnormal aggression

3.1. Hyperarousal-driven aggression

There are several psychopathologic states that are associated with increased arousal. In these disorders, aggressiveness is rather frequent, and appears to be tightly bound to hyperarousal symptoms. In chronic burnout, plasma glucocorticoids increased excessively during work hours, and this increase showed a positive correlation with post-work irritability (Melamed et al., 1996). Post-traumatic stress disorder is also associated with a wide array of stress-induced hyperarousal symptoms (increased sympathetic tone, adrenaline production, cortisol stress responses and autonomic reactions; Southwick et al., 1999; Elzinga et al., 2003; Bremner et al., 2003a,b), and hyperarousal symptoms were shown to correlate significantly with anger and hostility in this disorder (Beckham et al., 2002; Evans et al., 2003). Hyperarousal (tachycardia, sweating, flushing, tightness of the chest and affective reactions) were shown to correlate with the expression of sudden aggressive outbursts in two other disorders: depression and intermittent explosive disorder (Biondi et al., 2005; Eronen et al., 1998; Fava et al., 2000; Olvera, 2002; van Praag, 2001).

Hyperarousal appears to increase aggressive behavior in laboratory rodents as well, as rodents frustrated or "instigated" before the aggressive encounter show aggressive responses that overpass species-typical levels (Miczek et al., 2002; de Almeida and Miczek, 2002). This approach was based on earlier observations suggesting that the omission of scheduled rewards (frustration), or the exposure of rats to the sight and odor of an unfamiliar rat (instigation) increases the level of aggressiveness in a subsequent encounter with an intruder (Kelly, 1974; Potegal, 1992). As both manipulations (instigation and frustration) induce escalated levels of aggressiveness, laboratory rodents that are hyperaroused before the aggressive encounter might be used to study abnormal manifestations of aggressive behavior. The comparison of the effects of various pharmacological interventions suggested that the control of escalated and normal aggression is different. The 5-HT_{1B} receptor agonist anpirtoline appeared especially prone to suppress escalated aggression, suggesting that serotonergic mechanisms are strongly involved in controlling escalated aggression (Miczek et al., 2002, 2003; de Almeida and Miczek, 2002).

The involvement of glucocorticoid responses in chronic burnout-related aggressiveness is relatively clear, as post-work irritability and glucocorticoid plasma levels showed a significant correlation (Melamed et al., 1999). Unfortunately, the direct correlation between post-traumatic stress disorder-related aggressiveness and plasma glucocorticoid levels has not been systematically investigated. Nevertheless, urinary free cortisol excretion by post-traumatic stress disorder patients was positively correlated with both hyperarousal and aggressive behaviors in one study (De Bellis et al., 1999). The involvement of glucocorticoids in depression-related outbursts of anger has not been investigated either. However, depression is well known for its association with high basal glucocorticoid levels. Therefore, one cannot exclude that this endocrine background contributed to the irritability/anger attacks shown by such patients.

Despite the small number of directed studies on the relationship between plasma glucocorticoids and aggressiveness in the aforementioned disorders, there are a series of other studies that suggest that glucocorticoids are involved in excessive aggressive responses. In humans, plasma cortisol was shown to correlate positively with aggressive responses to insults (Cohen et al., 1996), nervousness and violence (Mazur, 1994), and self-assessed aggressive mood (Fibiger et al., 1984). In addition, the aggressive responses to an experimental provocation were higher in subjects showing higher plasma cortisol (Gerra et al., 1997, 2001). These data–although mostly obtained in psychologically healthy subjects–suggest that increased glucocorticoid responses might promote aggressiveness associated with hyperarousal. The pro-aggressive effect of glucocorticoids was also shown by a series of studies involving laboratory animals. Acute glucocorticoid treatments were shown to increase aggressiveness in several rodent species (Brain and Haug, 1992; Hayden-Hixon and Ferris, 1991; Haller et al., 1997; Mikics et al., 2004). Similar effects were obtained when glucocorticoids were locally applied to the hypothalamus (that is closely involved in the elicitation of biting attacks; Kruk, 1991) or infused into the cerebral ventricles, which suggests that the effect was centrally mediated (Hayden-Hixon and Ferris, 1991; Mikics et al., 2004). It was shown earlier that these effects of glucocorticoids are behavior specific, and cannot be reduced to a mere increase in arousal (Mikics et al., 2004, 2005). More recently, we have shown that there operates a positive feedback loop between brain centers involved in the control of aggression and those involved in the control of the stress response: aggressive interactions increase glucocorticoid production, whereas glucocorticoids on their turn promote aggressive behavior (Kruk et al., 2004). The "self-stimulation" of aggressive behavior via glucocorticoid secretion is possible because glucocorticoid plasma levels increase within minutes (Engelmann et al., 1996; Haller et al., 1995; Rodgers et al., 1999; Sgoifo et al., 1996), whereas aggressive contacts usually last tens of minutes and even hours in some cases. Thus, there is sufficient time for the pro-aggressive effect of glucocorticoids to be expressed. The consequences of the mutual facilitation by aggression and glucocorticoid production are dual: (i) acute stressors of any kind increase the probability of aggressive behavior, and (ii) the aggressive conflict per se (as a stressor) can stimulate aggressive behavior via increasing glucocorticoid production, which results in a vicious circle. One can hypothesize that the mutual facilitation between aggression and glucocorticoid production may promote abnormal forms of aggression (hyperarousal-driven aggression) when the glucocorticoid stress response is exaggerated.

Summary. Hyperarousal leads to increased aggressiveness in a variety of psychopathologies (e.g. chronic burnout, post-traumatic stress disorder, intermittent explosive disorder, depression). Laboratory rodents hyperaroused by instigation or frustration show escalated levels of aggression, which overpass

species-typical levels. Pharmacological experiments suggested that the control of escalated (hyperarousal-driven) and normal aggression is different, and the former depends to a large extent on serotonergic mechanisms involving 5- HT_{1B} receptors. Both human and laboratory findings suggest that increased glucocorticoid production is involved in the control of hyperarousal-driven abnormal aggression.

3.2. Hypoarousal-driven aggression

3.2.1. The human case

As shown above, aggressiveness in habitually violent offenders is characterized by low glucocorticoid levels, reduced adrenaline stress reactions, as well as reduced autonomic and skin conductance responsiveness to stress (Virkkunen, 1985; Dolan et al., 2001; Raine, 1996a,b; Herpertz et al., 2001; Brennan et al., 1997; Woodman and Hinton, 1978). In addition, antisocial personality disordered patients also show social phobia complex subtype (social fears) (Sareen et al., 2004). Glucocorticoid deficiency appears to play an outstanding role here, as it was shown to correlate negatively with aggressiveness and violence in a variety of patient groups that either showed antisocial personality disorder or its childhood antecedent conduct disorder (Dolan et al., 2001; McBurnett et al., 2000; Pajer et al., 2001; van Goozen et al., 1998; Vanyukov et al., 1993; Kariyawasam et al., 2002; Virkkunen, 1985). Noteworthy, low glucocorticoid levels (disregarded as pathogenic factors for a long time) were considered potentially harmful in many respects (Heim et al., 2000). The close relationship between low glucocorticoid levels and aggressiveness is indirectly supported by the interaction between early traumatic experiences and glucocorticoid production. Child maltreatment leads in many cases to a long-term increase in stress responsiveness, which in its turn increases the risk of mood and anxiety disorders (Heim and Nemeroff, 2001). Nevertheless, childhood trauma has opposite effects in a subgroup of those exposed, in which basal levels of glucocorticoids show a long lasting decrease (Gunnar and Vazquez, 2001; Cichetti and Rogosch, 2001; Rinne et al., 2002). These patients are prone to develop conduct and personality disorders. Noteworthy, personality disorders (and their childhood forms conduct and oppositional/defiant disorders) are believed to be largely due to child maltreatment (Bernstein et al., 1998; Haapaslo and Pokela, 1999).

3.2.2. Laboratory studies

It appears that correlations similar with those seen in humans were noticed in animals as well. Veenema et al. (2003a,b) noticed significant differences in the diurnal rhythm and the stress reactivity of the hypothalamus–pituitary–adrenocortical axis in mice selected for short and long attack latencies. The stress response was smaller in the short attack latency line; moreover, the response to chronic social stress was also considerably weaker in this line. In a similar fashion, larger aggressiveness correlated with lower glucocorticoid responses in birds selected for an active coping strategy (Carere et al., 2003). These data show that the genetic selection of animals for aggressive coping styles may result in phenotypes that are somewhat similar endocrinologically to violent antisocial personality-disordered humans. Importantly, mice selected for high aggressiveness showed a series of abnormal aggressive features (Sluyter et al., 2003). More conclusive evidence on the relationship between glucocorticoid deficiency and abnormal aggressiveness come from studies in which glucocorticoid secretion was experimentally stabilized at low levels by adrenalectomy and glucocorticoid pellets that ensured a low and stable level of plasma glucocorticoid levels. The mimicking of the endocrine condition that was associated with violence in antisocial personality disorder resulted in three important symptoms that appear similar with the symptoms seen in humans: (i) mismatched attack targeting, (ii) diminished autonomic arousal, and (iii) social deficits. Glucocorticoid-deficient rats preferentially attacked vulnerable targets (head, throat and belly) of their opponents. Such attacks were rare in controls (3–10% of the total number of attacks), whereas in glucocorticoid deficient rats their average share increased up to 70% (Haller et al., 2004). Noteworthy, acute treatment with glucocorticoids abolished this symptom (Haller et al., 2001). Vulnerable attacks are not unknown in normal rats, but these occur only in desperate situations, when the life of the subject is in danger (e.g. small rats show such attacks when introduced into a colony of large males; Blanchard and Blanchard, 1981). Females may also target attacks at vulnerable targets when defending their pups from intruding males (Parmigiani et al., 1988). In territorial aggressiveness, attack behavior follows certain “rules” that reduce the likelihood of serious harm. Such behavioral mechanisms are probably the results of an evolutionary pressure towards less dangerous forms of competitiveness, to avoid a high death toll of aggressive encounters. Glucocorticoid deficient rats appeared to disregard these rules, as they attacked body regions that are very susceptible to damage as contain vital sensory organs (e.g., the head), or are unprotected by bones and muscles like the back and flanks (which were preferentially targeted by controls). In addition to damage susceptibility, wounds on throat and belly are also susceptible to infections due to their proximity to soil. When rats were exposed to social encounters in their home cage or in an unfamiliar environment, they showed a considerable increase in their heart rate. The increase was less than a half in glucocorticoid deficient rats, showing that they not only displayed abnormal forms of attacks, but also autonomic hypoarousal. In addition, rats showed social deficits in the social interaction test, which did not appear to result from a general increase in anxiety, as they did not show signs of anxiety in other tests (elevated plus-maze and light/dark tests). Thus, glucocorticoid deficiency resulted in three important symptoms that are comparable with those seen in violent, antisocial disordered people: abnormal attack patterns, autonomic hypoarousal, and social deficits. Further experiments showed that abnormal aggressiveness is specifically linked to a chronic glucocorticoid deficiency. The transient decrease in glucocorticoid plasma levels by the glucocorticoid synthesis inhibitor metyrapone did not produce similar changes in aggressiveness (Mikics et al., 2004).

3.2.3. Mechanisms underlying hypoarousal-driven aggression in rats

So far, we conducted three independent studies in rats and a study in mice to elucidate the neural background of abnormal attacks associated with glucocorticoid deficiency.

In the first study, we assessed the patterns of aggression-induced neuronal activation by means of c-Fos immunocytochemistry. The study compared activation patterns seen in control and glucocorticoid-deficient rats exposed to resident–intruder conflicts (where the subjects of the study were residents) (Halasz et al., 2002). We studied c-Fos staining (as a marker of neuronal activation) from frontal regions to brainstem levels including the locus coeruleus and the raphe. In control rats, we obtained activation patterns consistent with earlier findings on the neural control of aggressive behavior. The most striking difference between control and glucocorticoid deficient rats concerned the paraventricular nucleus of the hypothalamus (involved in the control of the hypothalamus–pituitary–adrenocortical axis), and the central amygdala (involved in the control of fear, but also activated in predatory aggression; Siegel et al., 1999). The paraventricular nucleus of the hypothalamus was activated in both control and glucocorticoid deficient groups, but the activation was about twice as large in glucocorticoid deficient as in control rats. The central amygdala was not activated in control rats, but showed a dramatic activation in glucocorticoid deficient rats. The specific involvement of the central amygdala in abnormal forms of aggressiveness was recently confirmed by a study involving mice genetically selected for aggressiveness. The aggressiveness of these mice was considered abnormal according to a variety of criteria, and they also showed reduced glucocorticoid production in earlier experiments (Sluyter et al., 2003; Veenema et al., 2003a,b). Beyond some other differences, the mice of the highly aggressive strain (short attack latency mice) showed a dramatic fight-induced increase in central amygdala activation, which was not seen in the less aggressive strain (long attack latency mice) (Halász, Haller, de Boer, manuscript in preparation). Thus, it occurs that glucocorticoid deficiency-associated aggressiveness involves the strong activation of the central amygdala. Based on fighting-induced neuronal activation patterns seen in short attack latency mice (dramatic activation of the central amygdala and bed nucleus stria terminalis as well as a weaker activation of dorsal, and stronger activation of ventral subdivisions of the periaqueductal grey) we suggested that this strain shifted towards a predatory-like aggression (the changes outlined above are characteristic to predatory aggression; Siegel et al., 1999).

The second and third experiments performed in rats were motivated by the fact that c-Fos immunocytochemistry provides only rough information on neuronal processes activated during particular behaviors. As this methodology cannot differentiate neuron types, and the activation of different neuron types have dramatically different consequences for brain function, we have conducted experiments in which activated neurons were double stained for specific neuronal markers. In the raphe, serotonergic neurons (identified based on their tryptophan-hydroxylase content) were significantly activated by aggressive encounters, but a similar activation was seen in rats exposed to psychosocial contacts (in this case, intruders were separated from the subject by a perforated Plexiglas wall that enabled sensory but not physical contacts) (Haller et al., 2005). Thus, the activation of raphe serotonergic neurons was due to social contact but had no specific relation to aggression behavior. The most interesting result of this study was the dissociation of abnormal attack patterns from serotonergic activation (Fig. 1). “Normal” attacks (i.e. those aimed at non-vulnerable attack targets like the back and flanks) showed a significant negative correlation with the number of raphe serotonergic neurons activated by fights. This correlation was highly significant in control rats, but only marginally significant in

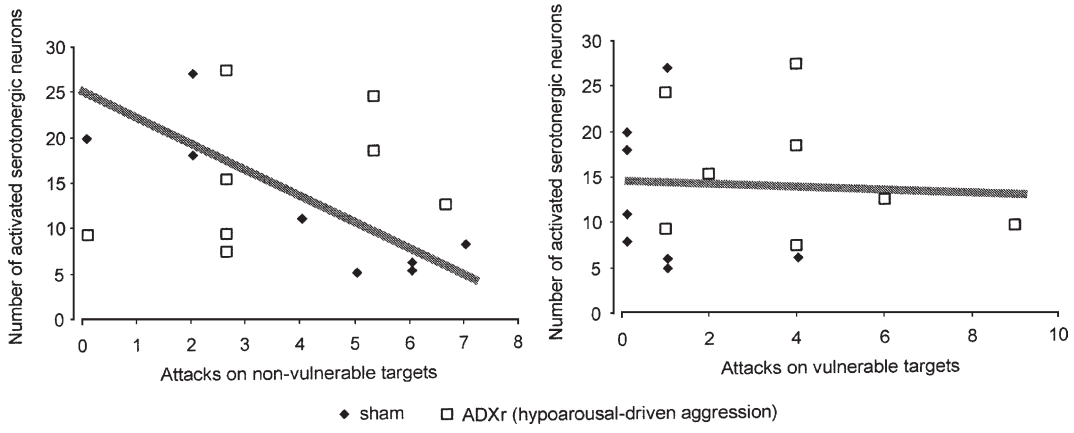

Fig. 1. Interactions between the activation of serotonergic neurons and attack patterns seen in control (sham operated) and glucocorticoid deficient (ADXr) rats. Control rats directed most of their attacks towards non-vulnerable targets (the back and flanks of their opponents). The frequency of such attacks correlated negatively with serotonergic activation (left hand panel, closed squares). Some of the attacks of glucocorticoid deficient rats were also directed towards non-vulnerable targets. These showed some correlation with serotonergic activation, but this was only marginally significant (left hand panel, open squares). A few control rats, and all glucocorticoid deficient rats directed attacks towards more vulnerable targets (head, throat and belly of their opponents). The frequency of these attacks did not correlate with the activation of raphe serotonergic neurons (right hand panel). These data show that serotonergic activation is negatively modulating attacks in control rats, but lost their aggression-controlling function in glucocorticoid deficiency-driven abnormal aggression.

glucocorticoid deficient rats. In contrast, no correlation was found between "abnormal" attacks (i.e. those aimed at the head, throat or belly), and the number of activated serotonergic neurons. The lack of correlation was observed in both control and glucocorticoid deficient rats. This study suggested that serotonergic neurons are involved in the control of normal, but are not involved in the control of abnormal attack patterns that were excessively increased in glucocorticoid deficient rats. The human relevance of this finding is given by the fact that serotonergic treatments (efficient in many other types of human aggression) appeared to be less efficient in aggressiveness associated with personality disorders. Serotonergic treatments (especially serotonin reuptake blockers) showed no or modest effects on aggressiveness in conduct and antisocial personality disorders (Bassarath, 2003; Kutcher et al., 1989; Mpofu, 2002; Pine and Cohen, 1999), in which disorders violence is frequently associated with glucocorticoid deficiency and/or hypoarousal. In some studies, personality disorders (including antisocial personality disorder) improved after selective serotonergic reuptake inhibitors (SSRIs) (Coccaro and Kavoussi, 1997). However, the improvement showed a positive correlation with D-fenfluramine responsiveness (Coccaro et al., 1997). Thus, mainly those patients responded well, which preserved good serotonin responsiveness. As the responsiveness to serotonergic agents (e.g. D-fenfluramine, buspirone) is largely diminished in aggressive antisocial personality disorders (Coccaro et al., 1996; Moss et al., 1990), the share of those responding well to SSRIs is probably low.

We have also assessed the activation of GABAergic interneuron subtypes in the prefrontal cortical areas of rats exposed to psychosocial contacts and fights (Halász, Tóth, Haller, manuscript in preparation). The reason of studying the prefrontal cortex was that lesions placed in this area increased aggressiveness in laboratory rodents (de Bruin et al., 1983), whereas the accidental damage of the cortex leads to abnormal aggression in humans (Hawkins and Trobst, 2000). In addition (and more importantly for the present study), hypoarousal-driven antisocial and aggressive behavior was shown to correlate with prefrontal deficits in humans (Raine, 2002). Cortical GABAergic interneurons play an important role in controlling the inputs and outputs of cortical principal cells, by this controlling the role that this brain area plays in brain function. This study cannot be presented in detail here, but we observed that the activation of prefrontal GABAergic interneurons and the execution of abnormal attacks were tightly related. This interaction was especially strong for CCK-containing basket cells that target the perisomatic region of principal (glutamatergic) neurons, and control the output of these neurons (Fig. 2). Glucocorticoid deficient rats showed a reduced CCK activation in two meanings: a generally reduced CCK expression, and a reduced share of CCK neuron activation. The negative correlation between CCK neuron activation and vulnerable attacks suggests that vulnerable attacks resulted from a deficit in the activation of these neurons.

3.2.4. Serotonergic neurotransmission as a mediator of glucocorticoid deficiency effects

The hypothalamus–pituitary–adrenocortical axis and the serotonergic system are tightly bound by various mechanisms. We suggest here that the interactions of these two systems are relevant for glucocorticoid deficiency induced abnormal aggressiveness. This assumption is partly based on our findings, as the role of serotonergic neurons in controlling aggressiveness was lost in glucocorticoid deficiency (Haller et al., 2005). In addition, a Multiple Regression analysis suggested that the occurrence of abnormal attacks was best predicted when both the activation of serotonergic neurons and that of the prefrontal cortex neurons were taken into account (Halasz, Toth, Hailer, unpublished findings). Beyond these findings, literature data also point towards an involvement of serotonergic neurotransmission in mediating the effects of glucocorticoid deficiency on aggression. An acute increase in plasma glucocorticoids inhibits the negative feed back of serotonin release (Meijer and de Kloet, 1998; Laaris et al., 1995), increases the synthesis of serotonin and the firing rate of raphe neurons (Neckers and Sze, 1975; Avanzino et al., 1984) and the serotonin content of the mesencephalon, hypothalamus, and amygdala (Telegdy and

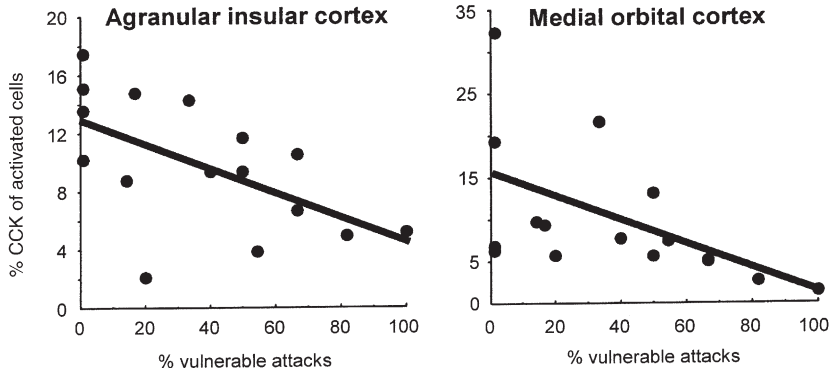

Fig. 2. Interactions between the ratio of vulnerable attacks and the activation of prefrontal CCK containing GABAergic interneurons. Control and glucocorticoid deficient rats were exposed to an intruder for 15 min. Glucocorticoid deficient rats showed a significantly larger ratio of attacks targeted towards vulnerable body parts of their opponents. Prefrontal CCK staining was weaker in glucocorticoid deficient rats as compared with controls. In addition, the share of activated CCK interneurons (i.e. those cells that showed both c-Fos and CCK signal) was lower in glucocorticoid-deficient than in control rats (data not shown here). As shown here, the activation of CCK containing interneurons was not only smaller in glucocorticoid-deficient rats, but also showed a negative correlation with vulnerable attacks. These data suggest that the glucocorticoid deficiency-induced deficit in prefrontal CCK interneuron activation is tightly bound to the executions of vulnerable attacks.

Vermes, 1975). These findings suggest that decreased glucocorticoid availability would reduce serotonergic neurotransmission. Indeed, adrenalectomy reduced the serotonin content of the mesencephalon, hypothalamus, amygdala, septum and hippocampus (Telegdy and Vermes, 1975), the level of serotonin and its metabolite 5-hydroxy indole acetic acid in the paraventricular nucleus of the hypothalamus and preoptic area (Jhanwar-Uniyal et al., 1987), and serotonin turnover in the hypothalamus and brainstem (Van Loon et al., 1982). In addition, low levels of glucocorticoids inhibited the response to serotonin in the hippocampus (Freo et al., 1992). Importantly for the present study, glucocorticoids have a permissive role on the serotonin-induced inhibition of the excitability of amygdalar neurons (Stutzmann et al., 1998). Via this mechanism, serotonin modulates the processing of sensory information within the lateral amygdala, and thus regulates amygdala-related functions. As the central amygdala (which receives inputs via the lateral amygdala) was involved in the glucocorticoid deficiency-induced abnormal forms of aggressiveness in rats (Halasz et al., 2002), the interaction between glucocorticoids, serotonin neurotransmission and amygdala function appears especially important for controlling glucocorticoid deficiency-induced abnormal aggression. Thus, glucocorticoid deficiency reduces serotonergic neurotransmission, which may result in a decreased impact of serotonin on the expression of aggressive behavior, which may result in the expression of abnormal aggression patterns. Noteworthy, the interaction between serotonin neurotransmission and aggressive behavior appears so robust, that it was postulated that serotonin is the primary molecular determinant of inter-male aggression, whereas other molecules appear to act indirectly through serotonin signaling (Nelson and Chiavegatto, 2001). As shown above, deficient serotonin input to the amygdala increases the excitability of the amygdala, which may explain the large increase in central amygdala activation seen in abnormally aggressive rats and mice. Certainly, the effects of glucocorticoids and serotonin go well beyond their interactions. Therefore, one can argue that the effects of glucocorticoids on aggressive behavior cannot fully be explained in terms of the serotonergic system. In addition, there are other hormones (e.g. testosterone) and other neural systems (e.g. noradrenergic neurotransmission) that affect aggressive behavior. Nevertheless, there is a striking consistency between the effects of the hypothalamus–pituitary–adrenocortical axis on hypoarousal-driven aggressive behavior on one hand and its effects on serotonergic neurotransmission on the other hand. This consistency suggests that the two systems control aggressive behavior in a close interaction, and their integrated rather then their separate study would help understanding abnormal manifestations of aggressive behavior.

3.2.5. Summary

Hypoarousal and low glucocorticoid levels seen in habitually violent antisocial personality disordered people (and in conduct disordered children) were suggested to be causally involved in their aggressiveness. When glucocorticoids were experimentally lowered in laboratory rats, abnormal patterns of attacks, hypoarousal in social challenges, and social deficits were noticed. Mice selected for aggressiveness, which exhibited abnormal forms of aggressiveness, also showed reduced glucocorticoid secretion. Taken together, these data demonstrate that reduced glucocorticoid levels result in abnormal patterns of aggressive behavior. Studies in laboratory rodents suggest that serotonergic neurotransmission as well as prefrontal brain regions (both being important modulators of normal aggressiveness) have no role in controlling hypoarousal-driven aggressiveness. In contrast, the central amygdala (which appears to have little role in controlling normal aggression) is robustly activated in glucocorticoid deficiency-induced abnormal aggression in both mice and rats. This suggests an important role of this brain center in the control of abnormal attacks. Based on earlier findings, we suggest that the glucocorticoid deficiency-induced reduction in serotonergic neurotransmission has a role in mediating the effects of glucocorticoid deficiency.

4. Conclusions

Human aggression associated with various psychopathologies is induced by a variety of conditions, is behaviorally variable, and shows differential pharmacological responsiveness. Thus, there are several types of human aggressiveness that can be considered abnormal due to their association with psychopathologies and due to other distinctive features. Recently, several laboratory models of abnormal aggression were proposed. These models can be used to study the neural backgrounds of abnormal aggressive behavior. Taken conjointly, human and laboratory findings suggest that glucocorticoids are deeply involved in the induction of mainly two types of abnormal aggression: that associated with hyperarousal (characteristic to intermittent explosive disorder, post-traumatic stress disorder, depression, chronic burnout, etc.) and that associated with hypoarousal (characteristic mainly to antisocial personality disorder and its childhood antecedent conduct disorder). Hyperarousal-driven aggressiveness appears to have at its root an excessive acute glucocorticoid stress response (and probably an exaggerated response of other stress-related systems), whereas hypoarousal-associated glucocorticoid deficits affect the function of the serotonergic system, prefrontal cortex and the central amygdala, with negative consequences for aggressive behavior. It occurs that the specific study of abnormal aspects of aggressive behavior would lead to important developments in understanding the mechanisms underlying abnormal aggressiveness.

Acknowledgments

This study was supported by a Harry Frank Guggenheim grant to J. Haller, and by the OTKA grant Nr. T 046785 EMB.

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