The link between aberrant hypothalamic-pituitary-adrenal axis activity during development and the emergence of aggression – Animal studies

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Abstract

Aggressive behavior is not uniform, including proactive and reactive forms of aggression. Aberrant functioning of the hypothalamic-pituitary-adrenal (HPA) axis is frequently associated with abnormal aggression. Here, we review the rodent literature in order to assess whether developmental abnormalities in the HPA axis can be causally linked with the emergence of abnormal aggression. We examine studies that involve genetic models and life challenges (e.g., early life stress, drug exposure) that course with developmental alterations in the HPA axis. Although the lack of systematic studies hinders development of an integrated model, existing evidence supports a U-shaped function regarding differences in HPA axis functioning during development and the emergence of aggressive phenotypes. Thus, developmentally low or high HPA axis reactivity are typically found to be aligned with the emergence of aggressive phenotypes; however, existing information is insufficient to causally link divergent HPA axis aberration with specific types of aggression. Progress in this field is needed to support interventions in children aimed at ameliorating social dysfunctions associated with aberrations in HPA axis function.

Keywords

Abnormal aggression; Aggression; Animal models; Behavior; Corticosterone; Drugs; Early life stress; HPA axis; Inbred strains; Mouse; Rat; Selective breeding;

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Aggression is a behavioral adaptation ubiquitously expressed throughout the animal kingdom. However, aggression is not uniformly expressed and may manifest in several forms. A general and widely accepted distinction discriminates between reactive, normally considered emotional-impulsive, and proactive, cold, gain-oriented, aggression (Haller, 2014a). Although the neurobiological mechanisms leading to the expression of these different types of aggression are still unclear, progress in this field is currently blooming (Blair, 2016; Waltes et al., 2015; Yang & Raine, 2009).

Altered functioning of the hypothalamus-pituitary-adrenal (HPA) axis has been frequently found to be associated to pathological forms of aggression. Along with the sympathetic nervous system (SNS), the activated HPA axis coordinates metabolic, behavioral and physiological responses to stressful challenges. Although findings from the human literature are not always consistent, probably due to the difficulties in systematizing its collection (timing, circadian characteristics, basal vs. reactive, etc.), substantial evidence indicates that individuals characterized by elevated levels of reactive aggression show heightened activation of the stress systems (Lopez-Duran et al., 2009). Conversely, one of the most consistently reported findings is that individuals with elevated affective psychopathic traits display blunted activation of the physiological stress systems (including blunted cortisol) to stressful situations (O'Leary et al., 2007; O'Leary et al., 2010; but see Johnson et al., 2015 for evidence in incarcerated male offenders showing that some psychopathic individuals show normal cortisol stress responses). Remarkably, substantial evidence indicates that similar alterations in the HPA axis are already observable during childhood (Fairchild et al., 2008; Hawes et al., 2009). Thus, HPA axis hypo-activity is frequently reported for children and adolescents with callous-unemotional traits (a large part of those diagnosed with conduct disorders, and those with a higher probability to show criminal behaviors at adulthood) (Loney et al., 2005; McBurnett et al., 2000; van Goozen et al., 2000 but see Gordis et al., 2006). On the other hand, HPA axis hyper-activity is observed in cases of child and adolescent antisocial behavior in those with low levels of callous-unemotional traits (Lopez-Duran et al., 2009).

An important and unresolved issue is whether such alterations in the stress systems, and particularly in the functioning of the HPA axis, are a mere correlate of the different types of aggressive behavior or, instead, play a causal role in the emergence of the respective aggressive phenotypes. Studies aimed at distinguishing the causal role of glucocorticoids – the final products of the activated HPA axis – in the regulation of aggressive behaviors are scarce. Most of the existing evidence that arrogates a key role of

glucocorticoids in aggression has been obtained by manipulating circulating levels of these hormones at adulthood (Kim & Haller, 2007; Haller, 2014b). Whether or not a similar picture would be observed when HPA axis alterations occur during development is a question that has not been systematically addressed. One study that applied injections of the HPA axis hormone, corticosterone, during the peripubertal period in rats reported increases in play fighting during adolescence and increased aggression at adulthood (Veenit et al., 2013), suggesting a causal role for enhanced corticosterone levels during development in the emergence of aggression. However, conclusions extracted from a single study are insufficient.

The purpose of this review is to analyze the relevant data from the animal literature that shed light on the potential link between deviation in normative HPA axis activity during development and the emergence of aggressive behaviors. We place a particular focus on rodent studies and, as most data has been gathered in males, we primarily review data obtained from male rodents. We first introduce the HPA axis and its developmental characteristics from a translational perspective in rodents and humans. Following on from previous reviews (Neumann et al., 2010; Veenema & Neumann, 2007), we focus on evidence obtained via genetic approaches, using lines of rodents selected either for HPA axis function or aggressiveness that deviate from normative levels throughout the individuals' life. We then explore the literature in which developmental variation in HPA axis function and aggression phenotypes are induced by manipulations occurring early in life, including stress and exposure to a diversity of drugs. Finally, we evaluate the knowledge extracted from the reviewed evidence regarding a potential link between developmental variation in HPA axis function and the emergence of aggressive phenotypes, and propose an integrative model that implies specific predictions that can be tested in future studies in the field.

1. The hypothalamus-pituitary-adrenal axis and its development

The HPA axis is a key physiological stress system. its activation involves a cascade of responses that starts with the secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) by the paraventricular nucleus (PVN) of the hypothalamus. In the pituitary, CRH and AVP stimulate the production and release of the adrenocorticotropic hormone (ACTH) into the bloodstream. When ACTH reaches the adrenal cortex, it stimulates the secretion and production of glucocorticoids (primarily cortisol in humans; corticosterone in a variety of rodents, including mice and rats). The HPA axis is inhibited by glucocorticoids, which exert negative feedback through actions on the hippocampus, the PVN and the pituitary (Ulrich-Lai and Herman, 2009).

Glucocorticoids act through two receptors systems, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). The GR is widely distributed in the brain and exhibits lower affinity for glucocorticoids compared to the MR (de Kloet et al., 2008). Upon glucocorticoid binding, corticosteroid receptors translocate to the nucleus, where they act as transcription factors. Through association with GR responsive elements, or through interactions with other transcription factors, these activated receptors induce or repress expression of genes critical for the modulation of many different processes, including inflammation, metabolism, behavior and cognition (Biddie et al., 2012; de Kloet, 2013). In addition to these genomic actions, membrane-bound MR and GR can also exert rapid, non-genomic, membrane-mediated effects (Groeneweg et al., 2011). Non-genomic glucocorticoid effects are thought to help encoding stress-related information as well as facilitating behaviors such as locomotion, aggression and other stress-related adaptive behaviors (de Kloet et al., 2008; Groeneweg et al., 2011; Makara & Haller, 2001; Sandi et al., 1996).

When translating developmental research studies between humans and rodents, it is important to note that there are important differences in the timing of the HPA axis development between these species (Lupien et al., 2009). For example, in humans, the HPA axis is highly responsive at birth whereas it is still under development during the first week of a rodent's life (Lupien et al., 2009). In rodents, the two weeks following birth are characterized by a "stress hypo-responsive period" (Schapiro, 1968), during which stress glucocorticoid responses have been reported to be largely blunted (Levine et al., 1994; Meaney et al., 1985). A comparable period of HPA axis hypo-responsivity may also exist in humans during childhood (Gunnar and Cheatham, 2003) and around puberty (Gunnar and Quevedo, 2007). It has been hypothesized that maternal care, social contact and parental buffering might be responsible for the maintenance of a hypo-responsive state both in rodents (Lupien et al., 2009) and humans (Gunnar and Cheatham, 2003). On the contrary, in rodents, during adolescence and early adulthood, the HPA axis is hyper-responsive due to an as yet underdeveloped negative feedback system (Klein and Romeo, 2013; McCormick and Mathews, 2010).

2. Genetic models of variation in HPA axis development in rodents: Consequences for aggression

Genetic animal models can help address the key question discussed in this review. More precisely, they allow the comparison of differences in the functioning of the HPA axis due to genetic factors with corresponding social behavior and aggression phenotypes. So far, existing data have been generated

through two main approaches: selective breeding of rodents to generate lines differing in the functioning of the HPA axis, and, comparison of inbred lines that were generated according to other traits but eventually differing in HPA axis function.

2.1. Rodents selectively bred for extremes in HPA axis activity

The selective breeding strategy starts from an outbred population. Animals displaying extremes in the 'target' phenotype are bred together for several generations after which the resulting lines ought to display stable differences in the phenotype of interest.

Mouse lines selected for extremes in HPA axis responsiveness to stress have been generated recently (Touma et al., 2008). Specifically, C57Bl/6 mice were selected and bred according to their plasma corticosterone response to 15 minutes of restraint stress, producing high-reactive (HR), low-reactive (LR) and intermediate-reactive (IR) lines (Touma et al., 2008). Once the lines were established, although they did not show differences in corticosterone levels at circadian nadir, HR mice had significantly higher diurnal corticosterone than the IR and LR lines (Touma et al., 2008). Following exposure to a stressor, and as compared to LR mice, HR animals were more reactive and showed higher activation of the paraventricular hypothalamic nucleus. Moreover, HR mice exhibited higher corticosterone responses to an ACTH injection and impaired negative feedback inhibition following a combined dexamethasone/CRH test (Heinzmann et al., 2014; Touma et al., 2008). The IR line displayed intermediate responses in these measurements. In one study, mice from these lines were tested for their aggressive behavior in the resident-intruder test. In this test, an unfamiliar mouse ('intruder') is introduced into the homecage of the experimental animal ('resident'). In this study, analyses were focused on the time the resident mouse took to attack the intruder – i.e., latency to attack, used as a proxy of aggressiveness – following the placement of the latter in the resident's cage. LR mice were the fastest to attack and 92% of them performed an attack within 300s vs only 42% of HR mice. The IR line behaved at an intermediate level, with 70% performing an attack within 300s (Touma et al., 2008). Therefore, low HPA axis responsiveness was linked to enhanced reactivity to attack an intruder conspecific and, hence, aggressiveness, in this study, while high HPA axis responsiveness had a negative link with aggression.

In addition to these mouse lines, there are several lines of rats that, although originally bred for extremes in behavioral traits relating to exploration or anxiety, show additional differences in HPA axis function and for which information about their aggressiveness has been gathered. These lines include: (i) the Roman high/low avoidance (RHA/RLA) lines, whose selection criterion was based on their ability to acquire a two-

way active avoidance task (Bignami, 1965); (ii) high/low anxiety-related behavior (HAB/LAB) lines, selected based on their behavior in the elevated plus maze and, then, crossbred in an early generation with lines selected for high and low active avoidance (Liebsch et al., 1998); and (iii) high/low responder lines (bHR/bLR), selected according to their locomotor behavior in a novel context (Stead et al., 2006). In each case, the line that shows enhanced HPA axis function, both in terms of diurnal corticosterone levels and in response to stressors, displayed higher levels of aggression than the counterpart line, or, in the case of HAB/LAB lines, in comparison to non-selected controls (Clinton et al., 2008; Kerman et al., 2011; Steimer et al., 1997; Steimer & Driscoll, 2003; Coppens et al., 2012; Coppens et al., 2013; Díaz-Morán et al., 2012 ; Landgraf et al., 1999; Neumann et al., 2005; Neumann et al., 2010b; Veenema et al., 2007 ; Beiderbeck et al., 2012). Although this is in contrast with the findings from mouse lines selected for divergent HPA axis responses described above, it is important to note that these studies did not always analyze the same parameters in the aggression test, nor was information routinely given about qualitative differences in aggressive behaviors, which potentially indicate presence of pathological reactions. For example, no information was provided as to whether attacks were delivered to vulnerable body parts or at a time when the intruder showed a submissive posture and, therefore, differences in aggression between the lines discussed here should be considered quantitative in nature.

2.2. Inbred rat strains

The second approach that we have chosen to discuss in this section is the comparison of phenotypes presented by inbred rat strains, which are generated by mating siblings across many consecutive generations. This process results in a strain in which only one version of each gene is present, and all animals are therefore genetically identical, somewhat akin to twins. Specifically, we discuss here strains of rats that present differences in the functioning of their HPA axis and that have been tested for their aggressive responses.

Such a comparison can be established, for example, between Fischer 344 (F344) and Lewis inbred rat strains, which were both derived from the Sprague Dawley strain. As noted by several studies, although these lines do not differ in basal corticosterone levels at diurnal nadir (Jongen-Rêlo et al., 2002), following exposure to stressors, such as restraint or tail shock, F344 rats had higher ACTH and corticosterone levels than Lewis rats (Gómez et al., 1998; Jongen-Rêlo et al., 2002). In agreement with this finding, F344 rats were found to have lower hippocampal GR expression, suggestive of less effective negative feedback regulation of HPA axis (Jongen-Rêlo et al., 2002). When these lines were compared for juvenile play

behavior paired with counterparts from either their same strain or Sprague Dawley, the F344 line showed less play fighting than Lewis juveniles (Siviy et al., 2003). These differences were not altered by cross-fostering, which indicates a strong genetic basis for these differential behaviors (Siviy et al., 2003). In line with these findings at juvenility, analysis of social behaviors at adulthood showed similar differences. Specifically, when exposed to a same strain partner in a neutral environment following two weeks of social isolation, F344 animals engaged in significantly fewer bouts of pinning and fighting with their opponent and launched fewer biting attacks than Lewis rats (Berton et al., 1997). In a subsequent resident-intruder test, although both F344 and Lewis rats were relatively unaggressive, F344 again were the ones that showed less aggressiveness, as they initiated fewer fights and spent a greater amount of time engaged in defensive behavior (Berton et al., 1997). Therefore, the strain with lower HPA axis responsiveness in this case showed enhanced aggression.

Another comparison can be drawn between normotensive Wistar-Kyoto (WKY) and spontaneously hypertensive (SHR) rat inbred strains, both derived from Wistar rats. These lines do not differ in their HPA axis hormone levels under basal conditions, but had divergent responses to stress – such as handling or restraint – with SHR rats showing higher plasma ACTH and corticosterone levels than WKY rats (Dickey et al., 2012; Roman et al., 2004). In this instance, the more HPA axis-reactive SHR rats are the ones reported to be more aggressive, when compared to WKY, across several experimental situations (Berton et al., 1997). Specifically, SHR were more aggressive: (i) in a colony-housing model, where they performed more attacks on novel intruders, and subordinates in the colony had significantly higher number of scars (Toot et al., 2004); (ii) in muricidal tests; (iii) when challenged with shock-induced fighting (Potegal and Myers, 1989).

These two examples of inbred rat strains indicate a mixed relationship between differential HPA axis function and the associated level of aggressive behavior that seems to depend on the background strain of the particular line. Specifically, in the strains derived from Sprague Dawley rats (i.e. Fischer 344 and Lewis strains), higher HPA axis reactivity is linked with decreased sociability and decreased aggressiveness. Conversely, in the strains derived from Wistar rats (i.e. WKY and SHR), higher HPA axis reactivity is associated with increased aggressiveness. Interestingly, in direct comparisons of Sprague Dawley-derived and Wistar-derived inbred strains, Wistar-derived rats have been shown to have higher HPA axis response to acute stress, less vulnerability to the effects of chronic social stress on bodyweight gain and higher overall aggressiveness (Berton et al., 1997). Although without the direct analyses of these different rats within a specific study, it is difficult to cross-compare findings; it is tempting to speculate the existence of

a U-shape effect for the results described above. Specifically, high aggression levels seem to be displayed by the Lewis and SHR strains showing, respectively, the lowest and highest HPA axis reactivity, while low aggression levels correspond to the strains (i.e., F344 and WKY) showing intermediate HPA axis responses.

3. Genetic models of variation in aggressiveness in rodents: Consequences for HPA axis function

A further approach to collect information about a potential link between developmental differences in HPA axis function and aggression is taking the converse strategy with regard to line selection to the ones described above. Here, we discuss data obtained from rodent lines selectively bred for extremes in aggressiveness and scrutinize whether they present significantly different HPA axis function. We review data from three mouse selection lines and one from rats.

One of the oldest documented lines selected for extremes on aggressiveness are the Turku aggressive (TA) and non-aggressive (TNA) mice, which were derived from an original cohort of Swiss albino outbred mice in 1959 (Sandnabba, 1985). As compared to TNA, TA mice have proven to be more aggressive in several parameters and testing situations. Thus, in a resident-intruder test, they perform more attacks, more threats and are less social than TNA mice (Caramaschi et al., 2008a). They also display reduced latency to attack a conspecific whether they are the resident, the intruder, or whether the social interaction takes place in a neutral cage (Nyberg et al., 2004). Importantly, TA mice are more likely to attack females in the homecage (Caramaschi et al., 2008a) or in a resident-intruder test (Nyberg et al., 2004), indicating presence of an abnormal aggressive phenotype in these mice. Although little is known about HPA axis function in these mice, some evidence indicates that TA mice had blunted diurnal peak corticosterone in comparison to TNA mice (Caramaschi et al., 2008b).

Other relevant lines include the low- (NC100) and high-aggressive (NC900) mice established from two sets of outbred ICR (Institute for Cancer Research) stock (Petitto et al., 1993). NC900 mice displayed significantly shorter attack latency, emitted more attacks, more sustained attack bouts, more threats, and were less social than NC100 (Caramaschi et al., 2008a). The aggressive phenotype of NC900 mice was not ameliorated by cross-fostering (Granger et al., 2001), indicating an intractability to environmental influences. Although there is limited information regarding HPA axis function in these mice, evidence shows that, relative to NC100 mice, NC900 have a lower basal (Petitto et al., 1993) and diurnal peak corticosterone levels (Granger et al., 1996). Curiously, this was found in conjunction with higher

hypothalamic CRH content in the same animals (Granger et al., 1996). This may suggest of blunted sensitivity of the pituitary to CRH tone in NC900 aggressive mice.

One of the best studied mouse lines in this context are the ones originally selected from wild house mice according to their short (SAL) or long (LAL) latency to attack a conspecific mouse (van Oortmerssen and Bakker, 1981). SAL mice displayed higher number of attacks and higher duration of aggressive behavior than LAL mice (Caramaschi et al., 2008a). Importantly, SAL mice have been described as abnormally aggressive as they attack females and anesthetized intruders, and ignore submissive postures of their opponents (Caramaschi et al., 2008a). Analysis of their HPA axis function indicates abnormal reactivity in SAL mice. Thus, although no differences between SAL and LAL mice were described under basal conditions (Veenema et al., 2003), SAL mice showed a flatter circadian corticosterone rhythmicity; the typical upshift of corticosterone during the dark phase being blunted in comparison to LAL mice (Korte et al., 1996). Furthermore, following exposure to novelty, administration of ACTH or forced swim stress, SAL mice displayed blunted corticosterone response relative to LAL mice (van Riel et al., 2002; Veenema et al., 2003), and mild psychosocial stress-induced corticosterone increases were short, as opposed to longer-lasting responses observed in LAL mice (Veenema et al., 2003).

Lines of rats derived from wild-caught Norway rats were selected according to their low ('domesticating') or high (maintenance of 'wild') aggressiveness toward a glove (Naumenko et al., 1989). Domesticated rats showed no aggressiveness toward humans by the 10th generation of selection (Plyusnina and Oskina, 1997). In terms of social behavior, wild rats emitted considerably more fighting bouts in shock-induced fighting tests than tame rats, but, at the 19th generation of selection did not display more inter-male aggression when not provoked by shock, nor were they more frequently muricidal (Naumenko et al., 1989). Later generations of the lines showed relatively higher inter-male aggressive behavior and lower social interaction in wild rats relative to domesticated rats (Gulevich et al., 2015). Regarding their HPA axis, wild line rats display higher basal corticosterone levels than tame rats (Gulevich et al., 2015; Naumenko et al., 1989). This finding was sustained when studying fecal matter obtained in the absence of any human interaction, which would presumably constitute a stressor, particularly to the wild line (Albert et al., 2008). Additionally, wild line rats showed higher corticosterone responses to novelty than domesticated rats, and had higher adrenal weight, indicative of both situational and general hyperactivity of the HPA axis (Naumenko et al., 1989; Plyusnina and Oskina, 1997).

The view depicted by the models discussed above suggests a species-dependent relation between aggressiveness and the HPA axis. The global message from mouse models is that selection for aggressive behaviors (that in in the case of TA, NC900 and SAL lines has co-segregated with pathological forms of aggression) were related with a blunted HPA axis activity and/or reactivity. However, the opposite pattern is observed in the rat lines, as the more aggressive line had higher HPA axis reactivity. However, an important caveat is that direct comparison of these models with other selection models is not possible since the definition of aggressive behaviors is relatively different between studies.

4. Developmental stress leading to variation in HPA axis function: Consequences for aggression

In addition to genetic selection, early life experiences can also have profound consequences on the development of the HPA axis. In particular, exposure to stressful experiences during different stages of development are known to have long-term consequences on HPA axis function and behavior. Early life stress can result in different psychopathologies, such as depression, anxiety, and alterations in social behaviors including changes in sociability and aggressiveness (Haller et al., 2014; Sandi & Haller, 2015; Veenema, 2009). The brain undergoes important changes during prenatal, postnatal and pubertal periods, which renders it highly vulnerable to stress (Lupien et al., 2009). Importantly, adverse experiences during early life and adolescence can also divert the development of the HPA axis which, in turn, can affect social behaviors (Sandi & Haller, 2015). We review here the relevant literature involving stress application at different early developmental periods in which an association between divergent HPA axis function and aggressiveness has been established.

4.1. Prenatal stress

Acute prenatal stress – administered on gestation days 10 and 19 – in an inbred strain of male rats (DA/Han) was found to result in increased stress-induced HPA axis reactivity (Patin et al., 2002) as well as reduced aggressiveness and increased submissiveness (Patin et al., 2005). Using a protocol of chronic prenatal stress, from gestation day 11 until delivery, in male Sprague-Dawley rats increased reactivity of the HPA axis following restraint stress was also observed. This was accompanied by decreased social play behavior (Morley-Fletcher et al., 2003). Conversely, chronic prenatal stress during the last week of pregnancy resulted in an increase of aggressive behaviors during a social interaction test, without effect on social play frequency, in juvenile male Wistar rats. Levels of corticosterone were not found to be different under basal conditions but were enhanced at diurnal peak and following exposure to forced-

swim stress (Koehl et al., 1999; Schroeder et al., 2013). In voles, different types of prenatal stress (including exposing pregnant females to either confrontation, immobilization or crowding on days 13, 14 and 15 of gestation) led to prolonged stress-induced activation of the HPA axis and increases in aggressiveness in male offspring (Marchlewska-Koj et al., 2003). Therefore, the opposite association between HPA axis reactivity resulting from prenatal stress exposure and aggression levels were found between rats and voles. Although it is not possible to conclude about species differences given the many additional differences in the studies discussed here (e.g., different nature, duration and timing of gestational stressors), higher HPA axis reactivity was found associated with lower aggression in rats, while it was related with higher aggression in voles.

4.2. Early postnatal stress

Separation of the young from the mother is one of the most used and best-studied models of early life adversity, aiming to mimic deficits observed in socially neglected children. We discuss here studies that have examined the consequence of this manipulation for HPA axis function and aggressive behaviors in rodents. Additionally, we mention relevant studies addressing the same question and evaluating similar parameters in monkeys.

In Wistar rats, maternal separation during the first two weeks of life led to a pattern of changes in endocrine and behavioral responses differential according to developmental stage (Veenema et al., 2006). Maternally-separated juvenile male rats showed an increase in HPA axis activity at basal level in the early dark phase, but no difference with regards to controls following social interaction. These juveniles exhibited increased play fighting and reduced submissive behaviors (Veenema and Neumann, 2009). However, when assessed at adulthood, HPA axis responsiveness was similar between stressed and control rats, both at baseline and after acute stressor. Maternally separated adult rats showed a faster increase in corticosterone levels after stress. In common with juvenile rats, adult animals were more aggressive during a resident-intruder test (Veenema et al., 2006).

In C57Bl/6 mice, however, maternal separation during the first two weeks of life is known to lead to increased reactivity of the HPA axis in response to stress (Parfitt et al., 2004), reduced play fighting in juvenility (Tsuda et al., 2011) and reduced intermale aggression at adulthood (Veenema et al., 2007). However, increased aggressiveness has been reported when a shorter maternal separation protocol was applied in Balb/C mice (Hohmann et al., 2013). To our knowledge, the HPA axis reactivity of these mice

has not been assessed, though behavioral similarities with C57Bl/6 mice led the authors to hypothesize HPA axis hyperactivity in this strain following stress (Hohmann et al., 2013).

In monkeys, juveniles reared in isolation were found to display elevated baseline cortisol levels, though acute stress-induced cortisol levels was not different to controls at adulthood (Meyer & Bowman, 1972; Sackett et al., 1973). Young monkeys, that were maternally-separated at birth, hand-reared for the first month and subsequently raised with same-age peers for the next 5 months, displayed higher levels of impulsive aggressive behaviors during play-fighting (Higley et al., 1996). Monkeys with this early life history were toward the bottom of the social hierarchy when housed with mother-reared peers (Suomi, 1997) and when challenged by a period of social separation, peer-reared monkeys exhibited extreme behaviors and higher HPA axis responses (Higley et al., 1991; Higley & Suomi, 1989). Furthermore, studies on monkeys maltreated by the mother during infancy have reported increased plasma cortisol levels in infant monkeys and exaggerated aggressive behaviors during adolescence (Howell et al., 2013). Conversely, other studies of peer-reared monkeys found low basal cortisol and low HPA axis response to stress as well as no differences in basal and stress-induced levels of cortisol (Clarke, 1993; Winslow et al., 2003; Champoux et al., 1989; Feng et al., 2011). Thus, no clear picture of the effects of peer-rearing stress on the HPA axis is evident. Recent studies have focused on explaining some of this variability, determining genetic factors and emphasizing the importance of gene-environment interactions linking stress, HPA axis and aggression (Novak et al., 2013). (Novak & Suomi, 2008) applied a rearing model in which monkeys were raised with an inanimate surrogate mother and provided daily exposure to playmates. Surrogate/peer-reared monkeys were more aggressive and displayed abnormal aggressive behaviors, as they did not respond to submissive postures of their opponents (Novak & Suomi, 2008). Furthermore, monkeys exhibited lower levels of circulating cortisol and showed blunted HPA axis response to a period of social separation (Capitanio et al., 2005; Davenport et al., 2003; Shannon et al., 2005; Shannon et al., 1998).

Overall, the picture arising from early stress protocols in different species emphasizes, once more, a complex relationship between variation in developmental HPA axis function and the emergence of aggression. Higher stress-induced HPA axis in rats was related to increased aggression, as previously described in several other models using this species. However, in monkeys, the two opposing patterns have been described, one that fits with the findings in rats and another one that links low HPA axis reactivity with higher aggression. Globally, all the findings summarized so far may be illustrated by a U-shaped relation between HPA axis regulation and the development of aggressive behaviors (Figure 1).

4.3. Peripubertal and adolescent stress

In humans, social neglect and bullying are two stressful experiences occurring in adolescence that are known to lead to hormonal alterations and behavioral deficits later in life (Tzanoulinou & Sandi, 2016). Corresponding rodent models, post-weaning social isolation and social subjugation, attempt to model alterations observed in humans (Haller et al., 2014). Exposure to fearful situations during peripuberty has been modeled with a peripubertal stress model of psychopathology (Márquez et al., 2013).

Studies employing post-weaning social isolation in male Wistar rats have reported that isolation from the point of weaning, over seven weeks, led to exaggerated corticosterone levels after aggressive encounters or social stress while not altering basal levels (Toth et al., 2011; Tulogdi et al., 2014). Isolated males also exhibited a pattern of abnormal or pathological aggression, including increased propensity to target their counterparts vulnerable body parts, such as throat, belly or head (Toth et al., 2011) and propelling unsignaled attacks toward their opponents (Toth et al., 2011). Moreover, socially deprived male rats showed increased defensive behaviors and initiated most of their attacks from defensive postures, suggesting aggression ambiguity. The aggressive behaviors of isolated rats were fragmented, with rapid switching from one behavior to another during resident-intruder encounters (Toth et al., 2011). A period of resocialization following isolation failed to ameliorate abnormal behaviors exhibited by socially deprived animals (Tulogdi et al., 2014). Interestingly, a study showed that the exposures to post-weaning social isolation shorter than seven weeks are sufficient to lead to alterations in social behaviors (Wall et al., 2012). When tested in late adolescence, following just four weeks of isolation, socially deprived Sprague Dawley rats showed enhanced play-fighting behavior and higher social interaction (Wall et al., 2012). This effect was found in both male and female rats. Chronicity of isolation appears to be a mediating factor, however. In mice, five days of peripubertal isolation did not lead to enhanced aggressive behavior, nor changes in HPA axis function, later in life (Pietropaolo et al., 2004). In summary, increased HPA axis reactivity was found to be associated with enhanced and pathological aggression in rats.

Bullying, or social abuse, is modelled in rodents via means of repeated social subjugation. Social subjugation of juvenile rats, by daily exposure to an aggressive adult, was shown to lead to enhanced basal corticosterone levels as well as exaggerated aggressive behaviors after both physical and social provocation, including towards larger opponents (Cunningham and McGinnis, 2008). In hamsters, juveniles (P26-38) exposed for 20 minutes daily in the homecage to an aggressive adult male (Delville et al., 1998), while not showing alterations in basal corticosterone levels, had increased stress-induced

corticosterone responses (Wommack and Delville, 2003). Subjugated hamsters attacked less intruders of similar size, but exhibited increased aggressive behavior (specifically, more biting) towards smaller opponents (Delville et al., 1998; Wommack & Delville, 2003; Wommack et al., 2003). Subjugated animals also showed premature transition from play-fighting behavior to adult-like patterns of attack, and displayed high levels of aggression at adulthood (Wommack et al., 2003). Other studies reported that hamsters subjugated during puberty (P26-38) showed high levels of aggression toward intruders and blunted release of cortisol (Ferris et al., 2005).

The peripubertal stress model of psychopathology developed originally in rats comprises a variable sequence of psychogenic, fear-inducing stressors, including exposure to elevated platform and predator odor, on seven scattered days across the peripubertal period (Márquez et al., 2013; Toledo-Rodriguez & Sandi, 2011). Although no difference in basal corticosterone was observed, peripubertal stress-exposed males and females had a blunted corticosterone response to stress and exhibited exaggerated aggression (Cordero et al., 2013; Márquez et al., 2013). In addition to several behavioral disturbances, male rats exposed to peripubertal stress showed evidence of pathological aggression at adulthood, as they showed increased intermale aggression, even towards juveniles and animals showing subordinate postures, and increased aggression towards a cohabitating female partners (Cordero et al., 2012; Márquez et al., 2013; Tzanoulinou et al., 2014). Although the corticosterone response induced by the resident-intruder test did not differ, the testosterone to corticosterone ratio was higher in peripubertal stress animals, which has been shown to be a marker of aggressive-impulsive behaviors in humans (Terburg et al., 2009).

Given all the findings reported above, we can argue that the relationship between stress and the development of alterations in HPA axis functions and aggressive behaviors that emerges from this data is complex. Again, rats stressed at peripuberty and/or adolescence tend to develop higher HPA axis reactivity and increased aggression. An exception seems to be for the peripubertal stress model in which lower HPA axis reactivity was linked to increased aggression. In this particular case, the discrepancy may be explained by considering the novelty of the stress stimulus used to assess HPA axis reactivity relative to the nature of the stress experienced earlier in life. Rats submitted to peripuberty stress, a stress consisting of repeated exposure to unpredictable and fearful situations, show blunted HPA axis response to a novel environment in adulthood (Márquez et al., 2013). By contrast, rats exposed to post-weaning social isolation showed HPA axis hyper-responsiveness to a social encounter, a wholly novel experience (Toth et al., 2011). This represents a more general problem in comparing across studies, and highlights the undue influence that single-point analyses of HPA axis function may have on interpretation of trends. Critically,

the effects seem to be highly dependent on the developmental period when stress is given, but also depend on the protocol and species used. Given the limited number of studies, further research is needed to disentangle the impact of different types of stress over time and at varying intervals of brain development in relation to aggressive behavior.

5. Developmental exposure to drugs: Effects on HPA axis function and aggression

In addition to genetic factors and early life stress, the HPA axis can be affected during developmental periods by exposure to a range of substances. We have a special focus here on drugs of abuse and antidepressants. The rationale to review the literature on drugs of abuse rests on the well-known, close and bidirectional interaction of the HPA axis and the mesolimbic dopamine system, the latter being a major site of action for these drugs (Koob & Kreek, 2007; Ungless et al., 2010). Moreover, mesolimbic dopamine plays a critical role in motivation towards both social and non-social stimuli (Salamone and Correa, 2012). Antidepressants are included in this section as there is documented evidence that they can affect neurodevelopmental trajectories of individuals.

5.1. Cocaine

Evidence indicates that prenatal cocaine exposure blunts HPA axis reactivity to novel and stress inducing stimuli in rats (Johns & Noonan, 1995; Johns et al., 1994), whilst also leading to enhanced aggressiveness (Johns & Noonan, 1995; Johns et al., 1994; Wood & Spear, 1998). Conversely, chronic cocaine exposure during adolescence appeared to give rise to a hyperactivity of the HPA axis in response to stress exposure (Alves et al., 2014) as well as leading to enhanced aggressiveness in both rats (Alves et al., 2014) and hamsters (Harrison et al., 2000; Jackson et al., 2005; Knyshevski et al., 2005).

5.2. Alcohol

Prenatal exposure to ethanol, via a variety of administration routes, gives rise to a hyperactive HPA axis responsiveness to a range of stressors (rats: Gabriel et al., 2000; Gangisetty et al., 2014; Kim et al., 1999 ; mice: Wieczorek et al., 2015). No differences in basal HPA axis tone, nor diurnal rhythmicity is evident however (rats: Glavas et al., 2007; mice: Wieczorek et al., 2015). Prenatally exposed rats demonstrated higher levels of play fighting and adult aggression relative to controls (Hamilton et al., 2010, 2014; Royalty, 1990).

There is little research exploring the effects of adolescent exposure to ethanol on either HPA axis function, aggression or both. The sole paper published thus far indicates that, in rats, there is dissociation in the effects of ethanol exposure between the early and late adolescent period (Varlinskaya et al., 2014). Specifically, early adolescent ethanol led to a decrease in social motivation, without concomitant alteration in HPA axis function, whereas late adolescent ethanol enhanced both fighting behavior and corticosterone response to this social challenge (Varlinskaya et al., 2014).

5.3. Cannabinoids

Perinatal administration of Δ9-THC or synthetic cannabinoid receptor type 1 (CB1R) agonists led to decreased HPA axis activity in adult male rats (del Arco et al., 2000; Rubio et al., 1995). Rats exposed to similar regimens of perinatal Δ9-THC displayed a reduction in play fighting at adolescence and in aggression at adulthood relative to vehicle-treated controls (Newsom & Kelly, 2008; Trezza et al., 2008). Exposure to a CB1R agonist at the postnatal time point only also led to reduced social interaction duration, including fighting behavior, when measured in late adolescence (O'Shea et al., 2006).

Conversely, pubertal exposure to CB1R agonists was associated with hyperactivity of the HPA axis in response to restraint stress in adult rats (Lee et al., 2014). Animals treated with a similar drug during adolescence showed alterations in social behavior in adulthood. Specifically, CB1R agonist exposed rats were more likely to behave defensively when attacked, as well as emitting more attacks and more pins themselves (Schneider and Koch, 2005).

5.4. Antidepressants

Research into the effect of antidepressant exposure during development on HPA axis and social function is limited. The existing literature indicates that pre and perinatal exposure to the selective serotonin re-uptake inhibitor (SSRI) class of antidepressant drugs gives rise to hyperactivity of the HPA axis in basal conditions as well as blunted corticosterone response to mild stress (Bourke et al., 2013). Mice treated prenatally with SSRIs displayed enhanced aggressive behaviors relative to vehicle-treated controls in a number of studies (Kiryanova & Dyck, 2014; Svirsky et al., 2015; Coleman et al., 1999). SSRIs have been shown to both decrease levels of circulating corticosterone and lead to impaired negative feedback regulation of corticosterone in rats (Gobinath et al., 2016; Pawluski et al., 2012). Route of administration, dose and time of testing influence the outcome. That noted, mice exposed to a similar treatment regimen

to the one that impaired HPA axis negative feedback regulation (Gobinath et al., 2016), demonstrated reduction in aggressive behavior at adulthood relative to control (Yu et al., 2014).

Exposure to addictive substances and medicines *in utero* can lead to both hypo and hyperactivity of the HPA axis later in life. Whether alterations in HPA axis activity in response to challenge represent general hypo- or hyper-function of the axis remains unknown. Drug-induced alteration of HPA axis function is associated with both increase and decreases in aggressive behavior depending on the drug in question. Effects of drug exposure during adolescence, on the other hand, render a more coherent picture. Across drug classes, evidence, though scant, indicates that adolescent exposure leads to enhanced HPA axis response to stressors, as well as enhanced aggression.

6. Discussion

We have reviewed the existing literature to assess the potential presence of a link between aberrations in the development of the HPA axis in a diversity of animal models and the emergence of aggression (summarized in Table 1.). The literature described is generated from genetically-selected and inbred strains of rodents, as well as on the effects of developmental exposure to stress or drugs of abuse. A major drawback in establishing any firm conclusion is the lack of systematic studies including equivalent manipulations (e.g., timing and duration of treatments) and common protocols for the measurement of the HPA axis and aggressive behaviors.

Thus, although a general unifying picture cannot be extracted from the reviewed data, there are certain commonalities that ought to be emphasized. We found several examples suggesting that aberrations towards abnormally low or abnormally high HPA axis functionality taking place during development are associated to increased aggression, frequently characterized by pathological features. Thus, the reviewed literature suggests the existence of a U-shape function between developmental HPA axis reactivity and the emergence of aggressive phenotypes (Figure 1). Note, however, that the U-shaped function presented here is naturally speculative, since the majority of models outlined have assessed HPA axis (re)activity and aggression in two groups only. It is thus important for future research to perform experiments taking into account an intermediate group. Of the studies that considered three groups, the HAB/LAB rat lines have come closest to supporting the hypothesized U-shape. In that case, both of the selected lines showed enhanced aggression relative to non-selected controls, and also demonstrated high and low HPA axis reactivity, respectively (Beiderbeck et al., 2012; Neumann et al., 2005, 2010). However, crucial information regarding the relative level of HPA axis reactivity in the control group has not been so far reported.

Therefore, the currently available data can only partially support our hypothesis, and further experiments considering three experimental groups are warranted.

Other data from the animal literature, not reviewed here, show that the direct manipulation of glucocorticoids at adulthood, leading to both abnormally low (Haller et al., 2004; Haller et al., 2001) or high (Haller et al., 1997; Kruk et al., 2004) glucocorticoid levels can lead to pathological aggression. This is found alongside alterations in the activity of brain regions and circuits implicated in the control of aggression (Haller, 2014a, 2014b). However, a critical issue is whether aberrant HPA axis has a causal implication in the development of aggressive phenotypes.

Research linking both aspects from a developmental perspective is scarce and it is thus difficult to outline a comprehensive view that implies any particular link between extremes in HPA axis variation and features of pathological aggression. Indeed, the HPA axis is not a single unit and various outcomes may arise from a unique modification in the system. For example, a decrease in corticosterone production may lead to differential behavioral outcomes whether it is associated with a hypersensitivity to a regulator of aggression or in a negative feedback of the systems. Discrepancies between studies and outcomes, in addition to the already mentioned differences in protocols and species, may arise from the inappropriately focal picture observable using single-point analyses of HPA axis function employed by many studies in the field. Traditionally, in line with the 'hypoarousal theory' of violence (Raine, 1996), blunted activation of the stress systems has been proposed to be particularly associated with symptoms of psychopathy. However, enhanced HPA axis reactivity was also related to pathological aggression in several rodent models (e.g., post-weaning social isolation; lines bred for high anxiety, and lines bred for maintenance of wildness), potentially mimicking emotional-impulsive types of aggression. Importantly, recent evidence in humans suggests that, even within individuals high in psychopathic traits, there might be subtypes presenting not only blunted, but also high HPA responses to stress (Johnson et al., 2015).

A key question arising from this review is what are the neurobiological mechanisms that could mediate the negative impact of developmental deviations in HPA axis activity on social behaviors. Although addressing this question is beyond the scope of the present review (for more information, see Sandi and Haller, 2015) and a precise answer will require further studies, existing evidence indicates that abnormal glucocorticoid levels during key developmental periods can have detrimental effects on brain structure and function (Jacobson and Sapolsky, 1991; Feldman and Weidenfeld, 1998; Matthews, 2000; Welberg et al., 2000; Seckl, 2004; Eiland and Romeo, 2013), including changes in brain regions involved in both the

regulation of the HPA axis and aggression (e.g. amygdala, prefrontal cortex, and hypothalamus) (Haller, 2004; Haller, 2014a; Biro et al., 2016). Additionally, neuromodulators that are critically implicated in aggression – e.g., serotonin (5-HT) – may also be affected by differential HPA axis development (Seckl, 2004).

It is important to note that various experimental results summarized in this review show some inconsistencies and their interpretation must be taken with great care. For example, the effects of stress highly depend on the developmental stage at the time of stress, and this may not be directly comparable between species (Matthews, 2000; Lupien et al., 2009). Some species give birth to immature young animals (e.g., rats and mice) while others deliver mature young ones (e.g., guinea pigs and primates). Immature young animals continue to display considerable higher rates of neuronal development after birth (Sapolsky and Meaney, 1986) and exhibit a higher glucocorticoid receptor sensitivity than the young of species with substantial rates of maturity at birth (Claman, 1972). In addition, it is important to note that the "stress hypo-responsive period" displayed by rats on the two weeks following birth has been interpreted from as an adaptation to enable proper brain development (Sapolsky & Meaney, 1986; Schmidt et al., 2005).

We should also note that critical differences in the ontogeny of aggression between the two rodent species reviewed here, namely rats and mice, may influence the conclusions drawn from the reviewed literature. For example, as summarized above, mice and rats exposed to maternal separation were found to display opposite patterns of aggression in the context of similar HPA axis reactivity (Boccia & Pedersen, 2001; Hohmann et al., 2013; Parfitt et al., 2004; Tsuda et al., 2011; Veenema et al., 2006; Veenema & Neumann, 2009). In particular, we know that these two species differ in their engagement in social play. Thus, rats engage heavily in play-fighting during the juvenile period (Pellis and McKenna, 1995) and, when deprived of such play experience they show aberrant social behaviors at adulthood, from hyper-defensiveness and failure to display appropriate submissive behavior, to exaggerated aggression (Potegal & Einon, 1989; Vanderschuren et al., 1997). These observations led to the hypothesis that engagement in social play was critical to the development of appropriate social behaviors (Vanderschuren et al. 1997, Pellis & Pellis 1998). However, as compared to rats, the social play repertoire of mice is impoverished (Pellis & Pasztor, 1999; Pellis & Pellis, 1998; Terranova et al., 1998). Accordingly, the social development, including aggressiveness, of these two species may not follow the same developmental pattern. Given that HPA axis activity relating to social play has been implicated in the effective learning of social interaction patterns

(Achterberg et al., 2014), elevated corticosterone levels during early life might influence the way in which play and aggressive behaviors are embedded differentially in these two species.

Additionally, the nature and duration of stressors given in different studies could also be critical in determining differences in aggression. It has been shown that various stressors, and other environmental challenges, do not elicit the same glucocorticoid secretion in rodents (Koolhaas et al., 2011) and that the quality of the stressor might also shape (or prime) future stress responses (Branchi et al., 2013). Additionally, the results of stress may be altered by housing conditions early in life. For example, it was shown that socially-enriched environments, while being stressful due to the inherent increase in social interactions, may actually be protective against stress and favor stronger cognitive abilities (D'Andrea et al., 2007; Huzard et al., 2015). It is thus important to take factors such as this into account in order to compare models but data remain too disparate to be able to draw clear conclusions from additional factors.

Furthermore, we should also note that one limitation with animal studies is the difficulty to clearly differentiate reactive and proactive types of aggression. Although various studies have reported abnormal forms of aggressive behaviors in rodents, it remains difficult to distinguish whether the motivation to aggress. As previously described (Haller, 2014a), "aggression is not a unitary phenomenon" and can be divided is various subtypes. It is often suggested that hypo-reactive (hypoaroused, "cold") individuals perform proactive aggression whereas hyper-reactive (hyperaroused, "hot") individuals display reactive aggression (Blair, 2001; Caramaschi, 2008a; Haller, 2014a; Provençal et al., 2015). Subdivision of aggression likely involves a complex brain network. One may suggest that distinct components are taking place in the emergence of aggressive behaviors: the onset of an aggressive bout, the intensity (low or highly aggressive), the nature of the outcome (normal or abnormal), and the type/context (reactive or proactive). The neural pathways responsible for such components might be distinct but interconnected, giving rise to the broad panel of aggressive responses reported in the literature. The different components of aggression could be altered independently by developmental changes. However, at present there is no systematic analysis of those different criteria allowing a precise description of the variations induced by stress at different developmental stages. Finally, the U-shape model may not only applicable to "aggressiveness" as a whole but to the different components of aggression, leading to a multi-dimensional model comprising multiple outcomes, as observed in the diversity of aggressive behaviors described in the literature.

A further limitation regards the difficulty in assessing whether the findings of studies using male animals generalize to females. The neurobiology underlying aggressive behavior, in terms of the downstream effects of signaling molecules, as well as in neuroanatomy, shows sexual dimorphism (Haller, 2014a). Additionally, the influence of the HPA axis on female aggression is little studied, an issue more deeply entrenched with regard to the developmental aspect under review here. From the available evidence, the relationship in females between altered HPA axis activity during development and later aggressiveness appears to align with the findings observed in males. For example, in rat lines originally bred for variation in anxiety-like behavior (HAB/LAB: Liebsch et al., 1998), female HAB rats showed enhanced aggressiveness. This was observed both in lactating and virgin females (Bosch & Neumann, 2010; de Jong et al., 2014). Though no differences in basal levels or in stress-induced levels of HPA axis activity were observed, the aggressive HAB line females showed blunted HPA axis responsiveness to an injection of CRH (Neumann et al., 1998). Additionally, in rats selectively-bred for aggressiveness toward humans ("wild" vs. "tame"), female wild rats were more aggressive than tame rats, and showed enhanced levels of corticosterone under basal conditions (Albert et al., 2008). This alignment also holds with regard to some developmental stress models. Indeed, peripubertally stressed female rats were found to show enhanced maternal aggression, as well as enhanced aggression prior to mating (Cordero et al., 2013). No differences in circulating corticosterone were found but increased basal vasopressin was observed (Cordero et al., 2013). In contrast, maternally-separated female rats showed reduced maternal aggression in the context of lower basal levels of corticosterone and enhanced responsiveness following stress (Aisa et al., 2008; Boccia & Pedersen, 2001; Koe et al., 2014; Slotten et al., 2006). Taken together these studies indicate that females showing alterations in HPA axis activity during development may display dysfunctional aggression later in life. Moreover, from the examples described above, it appears that female rats in which the HPA axis is under enhanced feedback-mediated inhibitory control may be more aggressive (Bosch & Neumann, 2010; de Jong et al., 2014; Neumann et al., 1998; Albert et al., 2008; Cordero et al., 2013; Boccia & Pedersen, 2001; Slotten et al., 2006; Koe et al., 2014; Aisa et al., 2008). These findings support a link between HPA axis hypo-responsiveness and enhanced aggression in females, in line with observations reviewed above in males. However, owing to the paucity of studies in females, we cannot draw any conclusion regarding the potential existence of a U-shape for them.

In conclusion, the reviewed evidence highlights a complex, but potentially critical link between developmental HPA axis activity and the development of social disturbances. In order to capture the causal link between these two elements in a time- and dose-controlled manner, future animal experiments should aim toward specific manipulation of HPA axis function using a variety of experimental approaches.

This research is much needed, given the suggestion that children with callous-unemotional traits might benefit from interventions capable of normalizing their blunted cortisol levels (van Goozen et al., 2007). Importantly, the data reviewed here indicate that genetic differences or other factors might critically affect neurodevelopmental trajectories influenced by aberrations –either high or low- in HPA axis function.

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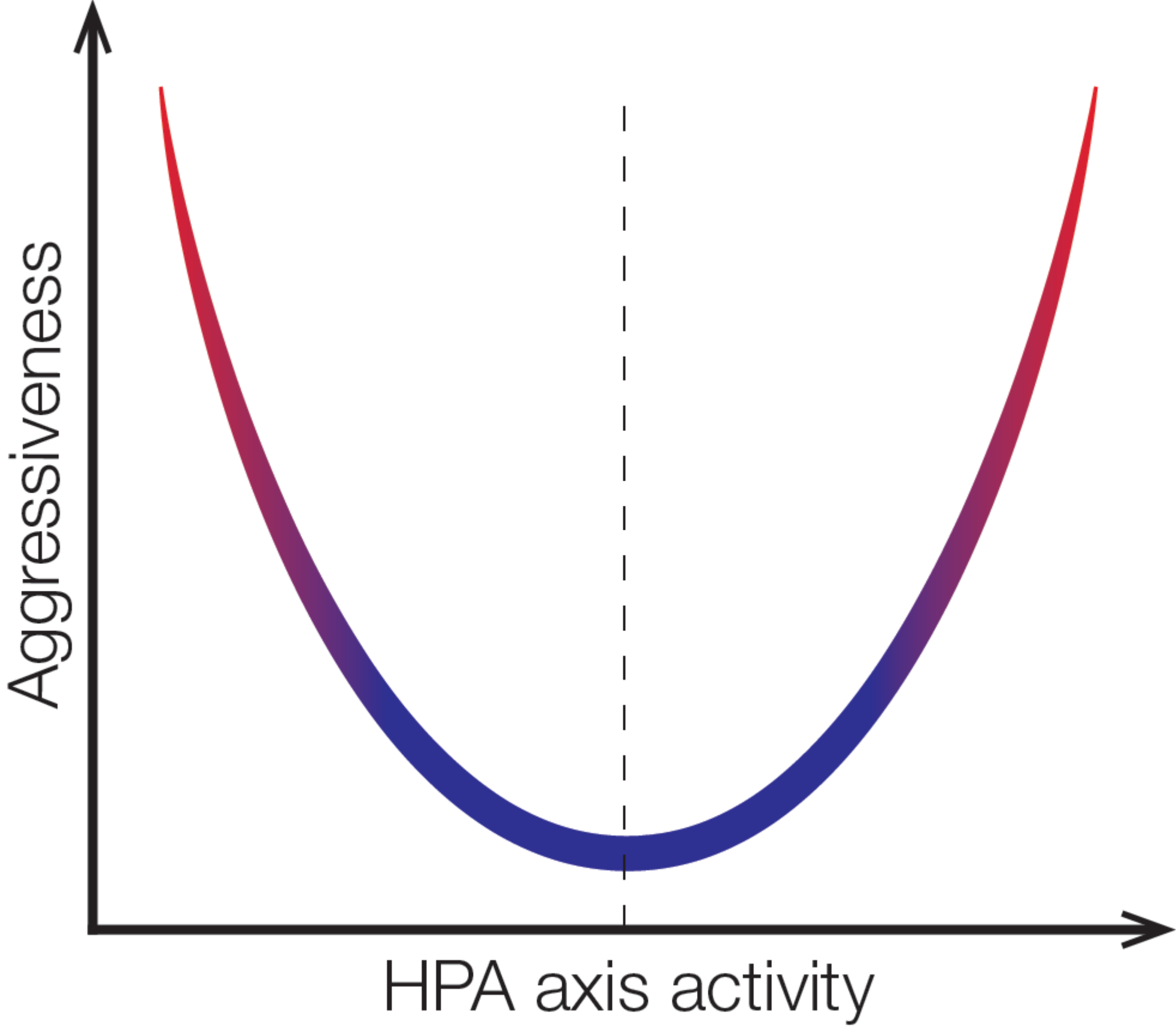
Figure and Table legends

Figure 1. U-shaped relationship between HPA axis functioning and aggressive behavior. HPA axis activity driven toward either hypo- or hyper-function is linked to exaggerated emission of aggression, often with abnormal features. Species, substrain and developmental stage also influence this relationship.

Table 1. Summary of literature describing the link between HPA axis function and aggressive behavior. ↑: represents an increase; ↓: a decrease; = not different; ?: not known; SHR: Spontaneously Hypertensive Rat; WKY: Wistar-Kyoto rat; F344: Fischer 344 rat; SD: Sprague-Dawley rat.


Aggressiveness
HPA axis activity

	Model or treatment	Developmental age	Species	HPA axis reactivity	Measurement time	Aggressiveness	References
Genetic models	Bred for extreme HPA axis reactivity	-	C57Bl/6 mice	LR: ↓	Diurnal peak + stress	Resident-intruder: ↑ (LR)	Heinzmann (2014), Touma et al. (2008)
	Bred for extreme anxiety traits	-	Rats	↑	Diurnal peak + stress	Resident-intruder: ↑ (low anxious) Abnormal aggression: ↑ (low anxious)	Beiderbeck et al. (2011), Landgraf et al. (1999), Neumann et al. (2005, 2010), Steimer et al. (2003), Veenema et al. (2006)
	Bred according to exploration	-	Rats	↑	Diurnal peak + stress	Resident-intruder: ↑ (high explorer)	Clinton et al. (2008), Kerman et al. (2011, 2012), Stead et al. (2006)
	Bred according to active avoidance	-	Rats	↑	Diurnal peak + stress	Resident-intruder: ↑ (low avoidance)	Bignami et al. (1965), Coppens et al. (2012, 2013), Diaz et al. (2012)
	Inbred strain derived from Sprague-Dawley (F344 and Lewis) and from Wistar (WKY and SHR)	-	Rats	SHR > WKY F344 > Lewis Wistar > SD	Stress	Play-fighting behavior: SHR, Lewis > WKY, F344 Resident-intruder: SHR, Lewis > F344, WKY Both: Wistar > Sprague Dawley	Berton et al. (1997), Dickey et al. (2012), Gomez et al. (1998), Jongen-Relo et al. (2002), Potegal et al. (1989), Roman et al. (2004), Siviy et al. (2003), Toot et al. (2004)
	Short-latency to attack (SAL) lines	-	Mice	↓	Dark phase + stress	Resident-intruder: ↑ Abnormal aggression: ↑	Caramaschi et al. (2008a), Korte et al. (1996), van Oortmerssen & Bakker (1981), van Riel et al.(2002), Veenema et al. (2003)
	High-aggressive NC900 lines	-	Mice	↓	Basal + diurnal peak	Resident-intruder: ↑	Caramaschi et al. (2008a), Granger et al. (1996, 2001), Petitto et al. (1993),
	Turku aggressive lines	-	Mice	↓	Diurnal peak	Resident-intruder: ↑ Abnormal aggression: ↑	Caramaschi et al. (2008a), Nyberg et al. (2004), Sandnabba et al. (1985)
	Wild-caught Norway lines	-	Rats	↑	Basal + stress	Resident-intruder: ↑ Shock-induced fighting: ↑	Albert et al. (2008), Gulevich et al. (2015), Naumenko et al. (1989), Nikulina et al. (1992), Plyusnina & Oskina (1997)
Early life stress models	Maternal stress during pregnancy	Prenatal	Inbred rats	↑	Stress	Social interaction: ↓	Patin et al. (2002, 2005)
		Prenatal	Sprague-Dawley	↑	Stress	Social interaction: ↓	Morley-Fletcher et al. (2003)
		Prenatal	Wistar	↑	Stress	Social interaction: ↑	Schroeder et al. (2013)
		Prenatal	Bank vole	↑	Stress	Aggression test: ↑	Marchlewska-Kloj et al. (2003)
	Maternal separation	Early life	Juvenile Wistar	↑	Basal	Play-fighting behavior: ↑	Veenema et al. (2006), Veenema & Neumann (2009)
		Early life	Adult Wistar	=	Basal + stress	Resident-intruder: ↑	Veenema et al. (2006)
		Early life	Long-Evans	↑	Stress	Maternal aggression: ↓	Boccia & Pedersen (2001)
		Early life	C57Bl/6 mice	↑	Stress	Maternal aggression: ↑ Play-fighting behavior: ↓ Resident-intruder: ↓	Parfitt et al. (2004), Tsuda et al. (2011), Veenema et al. (2007)
		Early life	Balb/C mice	↑	Stress	Resident-intruder: ↑	Hohmann et al. (2013)
	Isolated rearing	Early life	Juvenile monkeys	↑	Basal + stress	Play-fighting behavior: ↑	Higley et al. (1991, 1996), Higley & Suomi (1989), Suomi (1997)
		Early life	Adult monkeys	=	Stress	Playroom test: ↑	Meyer & Bowman (1972), Sackett et al. (1973)
	Peer-rearing	Early life	Monkeys	↓ or =	Basal + stress	Aggression test: ↑	Champoux et al. (1989), Clarke (1993), Feng et al. (2011), Winslow et al. (2003)
	Maternal maltreatment during infancy	Early life	Monkeys	↑	Basal	Aggression test: ↑	Howell et al. (2013)
	Surrogate/peer-rearing	Early life	Monkeys	↓	Basal + stress	Aggression test: ↑ Abnormal aggression: ↑	Capitanio et al. (2005), Davenport et al. (2003), Novak et al. (2013), Novak & Suomi (2008), Shannon et al. (1998, 2005)
	Post-weaning social isolation	Adolescence	Wistar	↑	Stress	Resident-intruder: ↑ Abnormal aggression: ↑	Haller et al. (2014), Toth et al. (2008), Toth et al. (2011), Tulogdi et al. (2014)
		Adolescence	Sprague-Dawley	↑	Stress	Play-fighting behavior: ↑ Social interaction: ↑	Wall et al. (2012)
	Repeated social subjugation	Adolescence	Golden hamsters	↑	Stress	Resident-intruder: ↑ (toward smaller opponents)	Delville et al. (1998), Wommack & Delville (2003), Wommack et al. (2003)
		Adolescence	Golden hamsters	↓	Stress	Resident-intruder: ↑	Ferris et al. (2005)
		Adolescence	Long-Evans	↑	Basal	Resident-intruder: ↑	Cunningham & McGinnis (2008)
	Peripuberty stress	Childhood and adolescence	Wistar	↓	Stress	Resident-intruder: ↑; Abnormal aggression: ↑ Aggression toward cohabitating female: ↑	Cordero et al. (2012), Cordero et al. (2013), Marquez et al. (2013), Toledo-Rodriguez & Sandi (2011)
Developmental exposure to drugs	Cocaine	Prenatal	Sprague-Dawley	↓	Stress	Resident-intruder: ↑ Maternal aggression: ↑	Johns et al. (1994), Johns & Noonan (1995), Wood & Spear (1998)
		Adolescence	Wistar rats & hamsters	↑	Stress	Resident-intruder: ↑	Alves et al. (2014), Harrison et al. (2000), Jackson et al. (2005), Knyshevksi et al. (2005)
	Alcohol	Prenatal	Rats and mice	↑	Stress	Play-fighting behavior: ↑ Resident-intruder: ↑	Gabriel et al. (2000), Gangisetty et al. (2014), Glavas et al. (2007), Kim et al. (1999), Wieczorek et al. (2015), Hamilton et al. (2010, 2014), Royalty (1990)
		Adolescence	Sprague-Dawley	↑	Stress	Play-fighting behavior: ↑	Varlinskaya et al. (2014)
	Cannabinoids	Perinatal	Wistar & Long-Evans	↓	Stress	Play-fighting behavior: ↓ Social interaction: ↓	Del Arco et al. (2000), Newsom & Kelly (2008), O'Shea et al. (2006), Rubio et al. (1995), Trezza et al. (2008)
		Adolescence	Wistar & Sprague-Dawley	↑	Stress	Social interaction: ↑	Lee et al. (2014), Schneider & Koch (2005)
	Antidepressants	Prenatal	Mice	?	-	Resident-intruder: ↑ Social interaction : ↑ or ↓	Bourke et al. (2013), Coleman et al. (1999), Kiryanova & Dyck (2014), Svirsky et al. (2015), Yu et al. (2014)
		Prenatal	Rats	↑ or ↓	Stress	?	Gobinath et al. (2016), Pawluski et al. (2012)

The link between aberrant hypothalamic-pituitary-adrenal axis activity during development and the emergence of aggression – Animal studies

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Abstract

Aggressive behavior is not uniform, including proactive and reactive forms of aggression. Aberrant functioning of the hypothalamic-pituitary-adrenal (HPA) axis is frequently associated with abnormal aggression. Here, we review the rodent literature in order to assess whether developmental abnormalities in the HPA axis can be causally linked with the emergence of abnormal aggression. We examine studies that involve genetic models and life challenges (e.g., early life stress, drug exposure) that course with developmental alterations in the HPA axis. Although the lack of systematic studies hinders development of an integrated model, existing evidence supports a U-shaped function regarding differences in HPA axis functioning during development and the emergence of aggressive phenotypes. Thus, developmentally low or high HPA axis reactivity are typically found to be aligned with the emergence of aggressive phenotypes; however, existing information is insufficient to causally link divergent HPA axis aberration with specific types of aggression. Progress in this field is needed to support interventions in children aimed at ameliorating social dysfunctions associated with aberrations in HPA axis function.

Keywords

Abnormal aggression; Aggression; Animal models; Behavior; Corticosterone; Drugs; Early life stress; HPA axis; Inbred strains; Mouse; Rat; Selective breeding;

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Aggression is a behavioral adaptation ubiquitously expressed throughout the animal kingdom. However, aggression is not uniformly expressed and may manifest in several forms. A general and widely accepted distinction discriminates between reactive, normally considered emotional-impulsive, and proactive, cold, gain-oriented, aggression (Haller, 2014a). Although the neurobiological mechanisms leading to the expression of these different types of aggression are still unclear, progress in this field is currently blooming (Blair, 2016; Waltes et al., 2015; Yang & Raine, 2009).

Altered functioning of the hypothalamus-pituitary-adrenal (HPA) axis has been frequently found to be associated to pathological forms of aggression. Along with the sympathetic nervous system (SNS), the activated HPA axis coordinates metabolic, behavioral and physiological responses to stressful challenges. Although findings from the human literature are not always consistent, probably due to the difficulties in systematizing its collection (timing, circadian characteristics, basal vs. reactive, etc.), substantial evidence indicates that individuals characterized by elevated levels of reactive aggression show heightened activation of the stress systems (Lopez-Duran et al., 2009). Conversely, one of the most consistently reported findings is that individuals with elevated affective psychopathic traits display blunted activation of the physiological stress systems (including blunted cortisol) to stressful situations (O'Leary et al., 2007; O'Leary et al., 2010; but see Johnson et al., 2015 for evidence in incarcerated male offenders showing that some psychopathic individuals show normal cortisol stress responses). Remarkably, substantial evidence indicates that similar alterations in the HPA axis are already observable during childhood (Fairchild et al., 2008; Hawes et al., 2009). Thus, HPA axis hypo-activity is frequently reported for children and adolescents with callous-unemotional traits (a large part of those diagnosed with conduct disorders, and those with a higher probability to show criminal behaviors at adulthood) (Loney et al., 2005; McBurnett et al., 2000; van Goozen et al., 2000 but see Gordis et al., 2006). On the other hand, HPA axis hyper-activity is observed in cases of child and adolescent antisocial behavior in those with low levels of callous-unemotional traits (Lopez-Duran et al., 2009).

An important and unresolved issue is whether such alterations in the stress systems, and particularly in the functioning of the HPA axis, are a mere correlate of the different types of aggressive behavior or, instead, play a causal role in the emergence of the respective aggressive phenotypes. Studies aimed at distinguishing the causal role of glucocorticoids – the final products of the activated HPA axis – in the regulation of aggressive behaviors are scarce. Most of the existing evidence that arrogates a key role of

glucocorticoids in aggression has been obtained by manipulating circulating levels of these hormones at adulthood (Kim & Haller, 2007; Haller, 2014b). Whether or not a similar picture would be observed when HPA axis alterations occur during development is a question that has not been systematically addressed. One study that applied injections of the HPA axis hormone, corticosterone, during the peripubertal period in rats reported increases in play fighting during adolescence and increased aggression at adulthood (Veenit et al., 2013), suggesting a causal role for enhanced corticosterone levels during development in the emergence of aggression. However, conclusions extracted from a single study are insufficient.

The purpose of this review is to analyze the relevant data from the animal literature that shed light on the potential link between deviation in normative HPA axis activity during development and the emergence of aggressive behaviors. We place a particular focus on rodent studies and, as most data has been gathered in males, we primarily review data obtained from male rodents. We first introduce the HPA axis and its developmental characteristics from a translational perspective in rodents and humans. Following on from previous reviews (Neumann et al., 2010; Veenema & Neumann, 2007), we focus on evidence obtained via genetic approaches, using lines of rodents selected either for HPA axis function or aggressiveness that deviate from normative levels throughout the individuals' life. We then explore the literature in which developmental variation in HPA axis function and aggression phenotypes are induced by manipulations occurring early in life, including stress and exposure to a diversity of drugs. Finally, we evaluate the knowledge extracted from the reviewed evidence regarding a potential link between developmental variation in HPA axis function and the emergence of aggressive phenotypes, and propose an integrative model that implies specific predictions that can be tested in future studies in the field.

1. The hypothalamus-pituitary-adrenal axis and its development

The HPA axis is a key physiological stress system. its activation involves a cascade of responses that starts with the secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) by the paraventricular nucleus (PVN) of the hypothalamus. In the pituitary, CRH and AVP stimulate the production and release of the adrenocorticotropic hormone (ACTH) into the bloodstream. When ACTH reaches the adrenal cortex, it stimulates the secretion and production of glucocorticoids (primarily cortisol in humans; corticosterone in a variety of rodents, including mice and rats). The HPA axis is inhibited by glucocorticoids, which exert negative feedback through actions on the hippocampus, the PVN and the pituitary (Ulrich-Lai and Herman, 2009).

Glucocorticoids act through two receptors systems, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). The GR is widely distributed in the brain and exhibits lower affinity for glucocorticoids compared to the MR (de Kloet et al., 2008). Upon glucocorticoid binding, corticosteroid receptors translocate to the nucleus, where they act as transcription factors. Through association with GR responsive elements, or through interactions with other transcription factors, these activated receptors induce or repress expression of genes critical for the modulation of many different processes, including inflammation, metabolism, behavior and cognition (Biddie et al., 2012; de Kloet, 2013). In addition to these genomic actions, membrane-bound MR and GR can also exert rapid, non-genomic, membrane-mediated effects (Groeneweg et al., 2011). Non-genomic glucocorticoid effects are thought to help encoding stress-related information as well as facilitating behaviors such as locomotion, aggression and other stress-related adaptive behaviors (de Kloet et al., 2008; Groeneweg et al., 2011; Makara & Haller, 2001; Sandi et al., 1996).

When translating developmental research studies between humans and rodents, it is important to note that there are important differences in the timing of the HPA axis development between these species (Lupien et al., 2009). For example, in humans, the HPA axis is highly responsive at birth whereas it is still under development during the first week of a rodent's life (Lupien et al., 2009). In rodents, the two weeks following birth are characterized by a "stress hypo-responsive period" (Schapiro, 1968), during which stress glucocorticoid responses have been reported to be largely blunted (Levine et al., 1994; Meaney et al., 1985). A comparable period of HPA axis hypo-responsivity may also exist in humans during childhood (Gunnar and Cheatham, 2003) and around puberty (Gunnar and Quevedo, 2007). It has been hypothesized that maternal care, social contact and parental buffering might be responsible for the maintenance of a hypo-responsive state both in rodents (Lupien et al., 2009) and humans (Gunnar and Cheatham, 2003). On the contrary, in rodents, during adolescence and early adulthood, the HPA axis is hyper-responsive due to an as yet underdeveloped negative feedback system (Klein and Romeo, 2013; McCormick and Mathews, 2010).

2. Genetic models of variation in HPA axis development in rodents: Consequences for aggression

Genetic animal models can help address the key question discussed in this review. More precisely, they allow the comparison of differences in the functioning of the HPA axis due to genetic factors with corresponding social behavior and aggression phenotypes. So far, existing data have been generated

through two main approaches: selective breeding of rodents to generate lines differing in the functioning of the HPA axis, and, comparison of inbred lines that were generated according to other traits but eventually differing in HPA axis function.

2.1. Rodents selectively bred for extremes in HPA axis activity

The selective breeding strategy starts from an outbred population. Animals displaying extremes in the 'target' phenotype are bred together for several generations after which the resulting lines ought to display stable differences in the phenotype of interest.

Mouse lines selected for extremes in HPA axis responsiveness to stress have been generated recently (Touma et al., 2008). Specifically, C57Bl/6 mice were selected and bred according to their plasma corticosterone response to 15 minutes of restraint stress, producing high-reactive (HR), low-reactive (LR) and intermediate-reactive (IR) lines (Touma et al., 2008). Once the lines were established, although they did not show differences in corticosterone levels at circadian nadir, HR mice had significantly higher diurnal corticosterone than the IR and LR lines (Touma et al., 2008). Following exposure to a stressor, and as compared to LR mice, HR animals were more reactive and showed higher activation of the paraventricular hypothalamic nucleus. Moreover, HR mice exhibited higher corticosterone responses to an ACTH injection and impaired negative feedback inhibition following a combined dexamethasone/CRH test (Heinzmann et al., 2014; Touma et al., 2008). The IR line displayed intermediate responses in these measurements. In one study, mice from these lines were tested for their aggressive behavior in the resident-intruder test. In this test, an unfamiliar mouse ('intruder') is introduced into the homecage of the experimental animal ('resident'). In this study, analyses were focused on the time the resident mouse took to attack the intruder – i.e., latency to attack, used as a proxy of aggressiveness – following the placement of the latter in the resident's cage. LR mice were the fastest to attack and 92% of them performed an attack within 300s vs only 42% of HR mice. The IR line behaved at an intermediate level, with 70% performing an attack within 300s (Touma et al., 2008). Therefore, low HPA axis responsiveness was linked to enhanced reactivity to attack an intruder conspecific and, hence, aggressiveness, in this study, while high HPA axis responsiveness had a negative link with aggression.

In addition to these mouse lines, there are several lines of rats that, although originally bred for extremes in behavioral traits relating to exploration or anxiety, show additional differences in HPA axis function and for which information about their aggressiveness has been gathered. These lines include: (i) the Roman high/low avoidance (RHA/RLA) lines, whose selection criterion was based on their ability to acquire a two-

way active avoidance task (Bignami, 1965); (ii) high/low anxiety-related behavior (HAB/LAB) lines, selected based on their behavior in the elevated plus maze and, then, crossbred in an early generation with lines selected for high and low active avoidance (Liebsch et al., 1998); and (iii) high/low responder lines (bHR/bLR), selected according to their locomotor behavior in a novel context (Stead et al., 2006). In each case, the line that shows enhanced HPA axis function, both in terms of diurnal corticosterone levels and in response to stressors, displayed higher levels of aggression than the counterpart line, or, in the case of HAB/LAB lines, in comparison to non-selected controls (Clinton et al., 2008; Kerman et al., 2011; Steimer et al., 1997; Steimer & Driscoll, 2003; Coppens et al., 2012; Coppens et al., 2013; Díaz-Morán et al., 2012 ; Landgraf et al., 1999; Neumann et al., 2005; Neumann et al., 2010b; Veenema et al., 2007 ; Beiderbeck et al., 2012). Although this is in contrast with the findings from mouse lines selected for divergent HPA axis responses described above, it is important to note that these studies did not always analyze the same parameters in the aggression test, nor was information routinely given about qualitative differences in aggressive behaviors, which potentially indicate presence of pathological reactions. For example, no information was provided as to whether attacks were delivered to vulnerable body parts or at a time when the intruder showed a submissive posture and, therefore, differences in aggression between the lines discussed here should be considered quantitative in nature.

2.2. Inbred rat strains

The second approach that we have chosen to discuss in this section is the comparison of phenotypes presented by inbred rat strains, which are generated by mating siblings across many consecutive generations. This process results in a strain in which only one version of each gene is present, and all animals are therefore genetically identical, somewhat akin to twins. Specifically, we discuss here strains of rats that present differences in the functioning of their HPA axis and that have been tested for their aggressive responses.

Such a comparison can be established, for example, between Fischer 344 (F344) and Lewis inbred rat strains, which were both derived from the Sprague Dawley strain. As noted by several studies, although these lines do not differ in basal corticosterone levels at diurnal nadir (Jongen-Rêlo et al., 2002), following exposure to stressors, such as restraint or tail shock, F344 rats had higher ACTH and corticosterone levels than Lewis rats (Gómez et al., 1998; Jongen-Rêlo et al., 2002). In agreement with this finding, F344 rats were found to have lower hippocampal GR expression, suggestive of less effective negative feedback regulation of HPA axis (Jongen-Rêlo et al., 2002). When these lines were compared for juvenile play

behavior paired with counterparts from either their same strain or Sprague Dawley, the F344 line showed less play fighting than Lewis juveniles (Siviy et al., 2003). These differences were not altered by cross-fostering, which indicates a strong genetic basis for these differential behaviors (Siviy et al., 2003). In line with these findings at juvenility, analysis of social behaviors at adulthood showed similar differences. Specifically, when exposed to a same strain partner in a neutral environment following two weeks of social isolation, F344 animals engaged in significantly fewer bouts of pinning and fighting with their opponent and launched fewer biting attacks than Lewis rats (Berton et al., 1997). In a subsequent resident-intruder test, although both F344 and Lewis rats were relatively unaggressive, F344 again were the ones that showed less aggressiveness, as they initiated fewer fights and spent a greater amount of time engaged in defensive behavior (Berton et al., 1997). Therefore, the strain with lower HPA axis responsiveness in this case showed enhanced aggression.

Another comparison can be drawn between normotensive Wistar-Kyoto (WKY) and spontaneously hypertensive (SHR) rat inbred strains, both derived from Wistar rats. These lines do not differ in their HPA axis hormone levels under basal conditions, but had divergent responses to stress – such as handling or restraint – with SHR rats showing higher plasma ACTH and corticosterone levels than WKY rats (Dickey et al., 2012; Roman et al., 2004). In this instance, the more HPA axis-reactive SHR rats are the ones reported to be more aggressive, when compared to WKY, across several experimental situations (Berton et al., 1997). Specifically, SHR were more aggressive: (i) in a colony-housing model, where they performed more attacks on novel intruders, and subordinates in the colony had significantly higher number of scars (Toot et al., 2004); (ii) in muricidal tests; (iii) when challenged with shock-induced fighting (Potegal and Myers, 1989).

These two examples of inbred rat strains indicate a mixed relationship between differential HPA axis function and the associated level of aggressive behavior that seems to depend on the background strain of the particular line. Specifically, in the strains derived from Sprague Dawley rats (i.e. Fischer 344 and Lewis strains), higher HPA axis reactivity is linked with decreased sociability and decreased aggressiveness. Conversely, in the strains derived from Wistar rats (i.e. WKY and SHR), higher HPA axis reactivity is associated with increased aggressiveness. Interestingly, in direct comparisons of Sprague Dawley-derived and Wistar-derived inbred strains, Wistar-derived rats have been shown to have higher HPA axis response to acute stress, less vulnerability to the effects of chronic social stress on bodyweight gain and higher overall aggressiveness (Berton et al., 1997). Although without the direct analyses of these different rats within a specific study, it is difficult to cross-compare findings; it is tempting to speculate the existence of

a U-shape effect for the results described above. Specifically, high aggression levels seem to be displayed by the Lewis and SHR strains showing, respectively, the lowest and highest HPA axis reactivity, while low aggression levels correspond to the strains (i.e., F344 and WKY) showing intermediate HPA axis responses.

3. Genetic models of variation in aggressiveness in rodents: Consequences for HPA axis function

A further approach to collect information about a potential link between developmental differences in HPA axis function and aggression is taking the converse strategy with regard to line selection to the ones described above. Here, we discuss data obtained from rodent lines selectively bred for extremes in aggressiveness and scrutinize whether they present significantly different HPA axis function. We review data from three mouse selection lines and one from rats.

One of the oldest documented lines selected for extremes on aggressiveness are the Turku aggressive (TA) and non-aggressive (TNA) mice, which were derived from an original cohort of Swiss albino outbred mice in 1959 (Sandnabba, 1985). As compared to TNA, TA mice have proven to be more aggressive in several parameters and testing situations. Thus, in a resident-intruder test, they perform more attacks, more threats and are less social than TNA mice (Caramaschi et al., 2008a). They also display reduced latency to attack a conspecific whether they are the resident, the intruder, or whether the social interaction takes place in a neutral cage (Nyberg et al., 2004). Importantly, TA mice are more likely to attack females in the homecage (Caramaschi et al., 2008a) or in a resident-intruder test (Nyberg et al., 2004), indicating presence of an abnormal aggressive phenotype in these mice. Although little is known about HPA axis function in these mice, some evidence indicates that TA mice had blunted diurnal peak corticosterone in comparison to TNA mice (Caramaschi et al., 2008b).

Other relevant lines include the low- (NC100) and high-aggressive (NC900) mice established from two sets of outbred ICR (Institute for Cancer Research) stock (Petitto et al., 1993). NC900 mice displayed significantly shorter attack latency, emitted more attacks, more sustained attack bouts, more threats, and were less social than NC100 (Caramaschi et al., 2008a). The aggressive phenotype of NC900 mice was not ameliorated by cross-fostering (Granger et al., 2001), indicating an intractability to environmental influences. Although there is limited information regarding HPA axis function in these mice, evidence shows that, relative to NC100 mice, NC900 have a lower basal (Petitto et al., 1993) and diurnal peak corticosterone levels (Granger et al., 1996). Curiously, this was found in conjunction with higher

hypothalamic CRH content in the same animals (Granger et al., 1996). This may suggest of blunted sensitivity of the pituitary to CRH tone in NC900 aggressive mice.

One of the best studied mouse lines in this context are the ones originally selected from wild house mice according to their short (SAL) or long (LAL) latency to attack a conspecific mouse (van Oortmerssen and Bakker, 1981). SAL mice displayed higher number of attacks and higher duration of aggressive behavior than LAL mice (Caramaschi et al., 2008a). Importantly, SAL mice have been described as abnormally aggressive as they attack females and anesthetized intruders, and ignore submissive postures of their opponents (Caramaschi et al., 2008a). Analysis of their HPA axis function indicates abnormal reactivity in SAL mice. Thus, although no differences between SAL and LAL mice were described under basal conditions (Veenema et al., 2003), SAL mice showed a flatter circadian corticosterone rhythmicity; the typical upshift of corticosterone during the dark phase being blunted in comparison to LAL mice (Korte et al., 1996). Furthermore, following exposure to novelty, administration of ACTH or forced swim stress, SAL mice displayed blunted corticosterone response relative to LAL mice (van Riel et al., 2002; Veenema et al., 2003), and mild psychosocial stress-induced corticosterone increases were short, as opposed to longer-lasting responses observed in LAL mice (Veenema et al., 2003).

Lines of rats derived from wild-caught Norway rats were selected according to their low ('domesticating') or high (maintenance of 'wild') aggressiveness toward a glove (Naumenko et al., 1989). Domesticated rats showed no aggressiveness toward humans by the 10th generation of selection (Plyusnina and Oskina, 1997). In terms of social behavior, wild rats emitted considerably more fighting bouts in shock-induced fighting tests than tame rats, but, at the 19th generation of selection did not display more inter-male aggression when not provoked by shock, nor were they more frequently muricidal (Naumenko et al., 1989). Later generations of the lines showed relatively higher inter-male aggressive behavior and lower social interaction in wild rats relative to domesticated rats (Gulevich et al., 2015). Regarding their HPA axis, wild line rats display higher basal corticosterone levels than tame rats (Gulevich et al., 2015; Naumenko et al., 1989). This finding was sustained when studying fecal matter obtained in the absence of any human interaction, which would presumably constitute a stressor, particularly to the wild line (Albert et al., 2008). Additionally, wild line rats showed higher corticosterone responses to novelty than domesticated rats, and had higher adrenal weight, indicative of both situational and general hyperactivity of the HPA axis (Naumenko et al., 1989; Plyusnina and Oskina, 1997).

The view depicted by the models discussed above suggests a species-dependent relation between aggressiveness and the HPA axis. The global message from mouse models is that selection for aggressive behaviors (that in in the case of TA, NC900 and SAL lines has co-segregated with pathological forms of aggression) were related with a blunted HPA axis activity and/or reactivity. However, the opposite pattern is observed in the rat lines, as the more aggressive line had higher HPA axis reactivity. However, an important caveat is that direct comparison of these models with other selection models is not possible since the definition of aggressive behaviors is relatively different between studies.

4. Developmental stress leading to variation in HPA axis function: Consequences for aggression

In addition to genetic selection, early life experiences can also have profound consequences on the development of the HPA axis. In particular, exposure to stressful experiences during different stages of development are known to have long-term consequences on HPA axis function and behavior. Early life stress can result in different psychopathologies, such as depression, anxiety, and alterations in social behaviors including changes in sociability and aggressiveness (Haller et al., 2014; Sandi & Haller, 2015; Veenema, 2009). The brain undergoes important changes during prenatal, postnatal and pubertal periods, which renders it highly vulnerable to stress (Lupien et al., 2009). Importantly, adverse experiences during early life and adolescence can also divert the development of the HPA axis which, in turn, can affect social behaviors (Sandi & Haller, 2015). We review here the relevant literature involving stress application at different early developmental periods in which an association between divergent HPA axis function and aggressiveness has been established.

4.1. Prenatal stress

Acute prenatal stress – administered on gestation days 10 and 19 – in an inbred strain of male rats (DA/Han) was found to result in increased stress-induced HPA axis reactivity (Patin et al., 2002) as well as reduced aggressiveness and increased submissiveness (Patin et al., 2005). Using a protocol of chronic prenatal stress, from gestation day 11 until delivery, in male Sprague-Dawley rats increased reactivity of the HPA axis following restraint stress was also observed. This was accompanied by decreased social play behavior (Morley-Fletcher et al., 2003). Conversely, chronic prenatal stress during the last week of pregnancy resulted in an increase of aggressive behaviors during a social interaction test, without effect on social play frequency, in juvenile male Wistar rats. Levels of corticosterone were not found to be different under basal conditions but were enhanced at diurnal peak and following exposure to forced-

swim stress (Koehl et al., 1999; Schroeder et al., 2013). In voles, different types of prenatal stress (including exposing pregnant females to either confrontation, immobilization or crowding on days 13, 14 and 15 of gestation) led to prolonged stress-induced activation of the HPA axis and increases in aggressiveness in male offspring (Marchlewska-Koj et al., 2003). Therefore, the opposite association between HPA axis reactivity resulting from prenatal stress exposure and aggression levels were found between rats and voles. Although it is not possible to conclude about species differences given the many additional differences in the studies discussed here (e.g., different nature, duration and timing of gestational stressors), higher HPA axis reactivity was found associated with lower aggression in rats, while it was related with higher aggression in voles.

4.2. Early postnatal stress

Separation of the young from the mother is one of the most used and best-studied models of early life adversity, aiming to mimic deficits observed in socially neglected children. We discuss here studies that have examined the consequence of this manipulation for HPA axis function and aggressive behaviors in rodents. Additionally, we mention relevant studies addressing the same question and evaluating similar parameters in monkeys.

In Wistar rats, maternal separation during the first two weeks of life led to a pattern of changes in endocrine and behavioral responses differential according to developmental stage (Veenema et al., 2006). Maternally-separated juvenile male rats showed an increase in HPA axis activity at basal level in the early dark phase, but no difference with regards to controls following social interaction. These juveniles exhibited increased play fighting and reduced submissive behaviors (Veenema and Neumann, 2009). However, when assessed at adulthood, HPA axis responsiveness was similar between stressed and control rats, both at baseline and after acute stressor. Maternally separated adult rats showed a faster increase in corticosterone levels after stress. In common with juvenile rats, adult animals were more aggressive during a resident-intruder test (Veenema et al., 2006).

In C57Bl/6 mice, however, maternal separation during the first two weeks of life is known to lead to increased reactivity of the HPA axis in response to stress (Parfitt et al., 2004), reduced play fighting in juvenility (Tsuda et al., 2011) and reduced intermale aggression at adulthood (Veenema et al., 2007). However, increased aggressiveness has been reported when a shorter maternal separation protocol was applied in Balb/C mice (Hohmann et al., 2013). To our knowledge, the HPA axis reactivity of these mice

has not been assessed, though behavioral similarities with C57Bl/6 mice led the authors to hypothesize HPA axis hyperactivity in this strain following stress (Hohmann et al., 2013).

In monkeys, juveniles reared in isolation were found to display elevated baseline cortisol levels, though acute stress-induced cortisol levels was not different to controls at adulthood (Meyer & Bowman, 1972; Sackett et al., 1973). Young monkeys, that were maternally-separated at birth, hand-reared for the first month and subsequently raised with same-age peers for the next 5 months, displayed higher levels of impulsive aggressive behaviors during play-fighting (Higley et al., 1996). Monkeys with this early life history were toward the bottom of the social hierarchy when housed with mother-reared peers (Suomi, 1997) and when challenged by a period of social separation, peer-reared monkeys exhibited extreme behaviors and higher HPA axis responses (Higley et al., 1991; Higley & Suomi, 1989). Furthermore, studies on monkeys maltreated by the mother during infancy have reported increased plasma cortisol levels in infant monkeys and exaggerated aggressive behaviors during adolescence (Howell et al., 2013). Conversely, other studies of peer-reared monkeys found low basal cortisol and low HPA axis response to stress as well as no differences in basal and stress-induced levels of cortisol (Clarke, 1993; Winslow et al., 2003; Champoux et al., 1989; Feng et al., 2011). Thus, no clear picture of the effects of peer-rearing stress on the HPA axis is evident. Recent studies have focused on explaining some of this variability, determining genetic factors and emphasizing the importance of gene-environment interactions linking stress, HPA axis and aggression (Novak et al., 2013). (Novak & Suomi, 2008) applied a rearing model in which monkeys were raised with an inanimate surrogate mother and provided daily exposure to playmates. Surrogate/peer-reared monkeys were more aggressive and displayed abnormal aggressive behaviors, as they did not respond to submissive postures of their opponents (Novak & Suomi, 2008). Furthermore, monkeys exhibited lower levels of circulating cortisol and showed blunted HPA axis response to a period of social separation (Capitanio et al., 2005; Davenport et al., 2003; Shannon et al., 2005; Shannon et al., 1998).

Overall, the picture arising from early stress protocols in different species emphasizes, once more, a complex relationship between variation in developmental HPA axis function and the emergence of aggression. Higher stress-induced HPA axis in rats was related to increased aggression, as previously described in several other models using this species. However, in monkeys, the two opposing patterns have been described, one that fits with the findings in rats and another one that links low HPA axis reactivity with higher aggression. Globally, all the findings summarized so far may be illustrated by a U-shaped relation between HPA axis regulation and the development of aggressive behaviors (Figure 1).

4.3. Peripubertal and adolescent stress

In humans, social neglect and bullying are two stressful experiences occurring in adolescence that are known to lead to hormonal alterations and behavioral deficits later in life (Tzanoulinou & Sandi, 2016). Corresponding rodent models, post-weaning social isolation and social subjugation, attempt to model alterations observed in humans (Haller et al., 2014). Exposure to fearful situations during peripuberty has been modeled with a peripubertal stress model of psychopathology (Márquez et al., 2013).

Studies employing post-weaning social isolation in male Wistar rats have reported that isolation from the point of weaning, over seven weeks, led to exaggerated corticosterone levels after aggressive encounters or social stress while not altering basal levels (Toth et al., 2011; Tulogdi et al., 2014). Isolated males also exhibited a pattern of abnormal or pathological aggression, including increased propensity to target their counterparts vulnerable body parts, such as throat, belly or head (Toth et al., 2011) and propelling unsignaled attacks toward their opponents (Toth et al., 2011). Moreover, socially deprived male rats showed increased defensive behaviors and initiated most of their attacks from defensive postures, suggesting aggression ambiguity. The aggressive behaviors of isolated rats were fragmented, with rapid switching from one behavior to another during resident-intruder encounters (Toth et al., 2011). A period of resocialization following isolation failed to ameliorate abnormal behaviors exhibited by socially deprived animals (Tulogdi et al., 2014). Interestingly, a study showed that the exposures to post-weaning social isolation shorter than seven weeks are sufficient to lead to alterations in social behaviors (Wall et al., 2012). When tested in late adolescence, following just four weeks of isolation, socially deprived Sprague Dawley rats showed enhanced play-fighting behavior and higher social interaction (Wall et al., 2012). This effect was found in both male and female rats. Chronicity of isolation appears to be a mediating factor, however. In mice, five days of peripubertal isolation did not lead to enhanced aggressive behavior, nor changes in HPA axis function, later in life (Pietropaolo et al., 2004). In summary, increased HPA axis reactivity was found to be associated with enhanced and pathological aggression in rats.

Bullying, or social abuse, is modelled in rodents via means of repeated social subjugation. Social subjugation of juvenile rats, by daily exposure to an aggressive adult, was shown to lead to enhanced basal corticosterone levels as well as exaggerated aggressive behaviors after both physical and social provocation, including towards larger opponents (Cunningham and McGinnis, 2008). In hamsters, juveniles (P26-38) exposed for 20 minutes daily in the homecage to an aggressive adult male (Delville et al., 1998), while not showing alterations in basal corticosterone levels, had increased stress-induced

corticosterone responses (Wommack and Delville, 2003). Subjugated hamsters attacked less intruders of similar size, but exhibited increased aggressive behavior (specifically, more biting) towards smaller opponents (Delville et al., 1998; Wommack & Delville, 2003; Wommack et al., 2003). Subjugated animals also showed premature transition from play-fighting behavior to adult-like patterns of attack, and displayed high levels of aggression at adulthood (Wommack et al., 2003). Other studies reported that hamsters subjugated during puberty (P26-38) showed high levels of aggression toward intruders and blunted release of cortisol (Ferris et al., 2005).

The peripubertal stress model of psychopathology developed originally in rats comprises a variable sequence of psychogenic, fear-inducing stressors, including exposure to elevated platform and predator odor, on seven scattered days across the peripubertal period (Márquez et al., 2013; Toledo-Rodriguez & Sandi, 2011). Although no difference in basal corticosterone was observed, peripubertal stress-exposed males and females had a blunted corticosterone response to stress and exhibited exaggerated aggression (Cordero et al., 2013; Márquez et al., 2013). In addition to several behavioral disturbances, male rats exposed to peripubertal stress showed evidence of pathological aggression at adulthood, as they showed increased intermale aggression, even towards juveniles and animals showing subordinate postures, and increased aggression towards a cohabitating female partners (Cordero et al., 2012; Márquez et al., 2013; Tzanoulinou et al., 2014). Although the corticosterone response induced by the resident-intruder test did not differ, the testosterone to corticosterone ratio was higher in peripubertal stress animals, which has been shown to be a marker of aggressive-impulsive behaviors in humans (Terburg et al., 2009).

Given all the findings reported above, we can argue that the relationship between stress and the development of alterations in HPA axis functions and aggressive behaviors that emerges from this data is complex. Again, rats stressed at peripuberty and/or adolescence tend to develop higher HPA axis reactivity and increased aggression. An exception seems to be for the peripubertal stress model in which lower HPA axis reactivity was linked to increased aggression. In this particular case, the discrepancy may be explained by considering the novelty of the stress stimulus used to assess HPA axis reactivity relative to the nature of the stress experienced earlier in life. Rats submitted to peripuberty stress, a stress consisting of repeated exposure to unpredictable and fearful situations, show blunted HPA axis response to a novel environment in adulthood (Márquez et al., 2013). By contrast, rats exposed to post-weaning social isolation showed HPA axis hyper-responsiveness to a social encounter, a wholly novel experience (Toth et al., 2011). This represents a more general problem in comparing across studies, and highlights the undue influence that single-point analyses of HPA axis function may have on interpretation of trends. Critically,

the effects seem to be highly dependent on the developmental period when stress is given, but also depend on the protocol and species used. Given the limited number of studies, further research is needed to disentangle the impact of different types of stress over time and at varying intervals of brain development in relation to aggressive behavior.

5. Developmental exposure to drugs: Effects on HPA axis function and aggression

In addition to genetic factors and early life stress, the HPA axis can be affected during developmental periods by exposure to a range of substances. We have a special focus here on drugs of abuse and antidepressants. The rationale to review the literature on drugs of abuse rests on the well-known, close and bidirectional interaction of the HPA axis and the mesolimbic dopamine system, the latter being a major site of action for these drugs (Koob & Kreek, 2007; Ungless et al., 2010). Moreover, mesolimbic dopamine plays a critical role in motivation towards both social and non-social stimuli (Salamone and Correa, 2012). Antidepressants are included in this section as there is documented evidence that they can affect neurodevelopmental trajectories of individuals.

5.1. Cocaine

Evidence indicates that prenatal cocaine exposure blunts HPA axis reactivity to novel and stress inducing stimuli in rats (Johns & Noonan, 1995; Johns et al., 1994), whilst also leading to enhanced aggressiveness (Johns & Noonan, 1995; Johns et al., 1994; Wood & Spear, 1998). Conversely, chronic cocaine exposure during adolescence appeared to give rise to a hyperactivity of the HPA axis in response to stress exposure (Alves et al., 2014) as well as leading to enhanced aggressiveness in both rats (Alves et al., 2014) and hamsters (Harrison et al., 2000; Jackson et al., 2005; Knyshevski et al., 2005).

5.2. Alcohol

Prenatal exposure to ethanol, via a variety of administration routes, gives rise to a hyperactive HPA axis responsiveness to a range of stressors (rats: Gabriel et al., 2000; Gangisetty et al., 2014; Kim et al., 1999 ; mice: Wieczorek et al., 2015). No differences in basal HPA axis tone, nor diurnal rhythmicity is evident however (rats: Glavas et al., 2007; mice: Wieczorek et al., 2015). Prenatally exposed rats demonstrated higher levels of play fighting and adult aggression relative to controls (Hamilton et al., 2010, 2014; Royalty, 1990).

There is little research exploring the effects of adolescent exposure to ethanol on either HPA axis function, aggression or both. The sole paper published thus far indicates that, in rats, there is dissociation in the effects of ethanol exposure between the early and late adolescent period (Varlinskaya et al., 2014). Specifically, early adolescent ethanol led to a decrease in social motivation, without concomitant alteration in HPA axis function, whereas late adolescent ethanol enhanced both fighting behavior and corticosterone response to this social challenge (Varlinskaya et al., 2014).

5.3. Cannabinoids

Perinatal administration of Δ9-THC or synthetic cannabinoid receptor type 1 (CB1R) agonists led to decreased HPA axis activity in adult male rats (del Arco et al., 2000; Rubio et al., 1995). Rats exposed to similar regimens of perinatal Δ9-THC displayed a reduction in play fighting at adolescence and in aggression at adulthood relative to vehicle-treated controls (Newsom & Kelly, 2008; Trezza et al., 2008). Exposure to a CB1R agonist at the postnatal time point only also led to reduced social interaction duration, including fighting behavior, when measured in late adolescence (O'Shea et al., 2006).

Conversely, pubertal exposure to CB1R agonists was associated with hyperactivity of the HPA axis in response to restraint stress in adult rats (Lee et al., 2014). Animals treated with a similar drug during adolescence showed alterations in social behavior in adulthood. Specifically, CB1R agonist exposed rats were more likely to behave defensively when attacked, as well as emitting more attacks and more pins themselves (Schneider and Koch, 2005).

5.4. Antidepressants

Research into the effect of antidepressant exposure during development on HPA axis and social function is limited. The existing literature indicates that pre and perinatal exposure to the selective serotonin re-uptake inhibitor (SSRI) class of antidepressant drugs gives rise to hyperactivity of the HPA axis in basal conditions as well as blunted corticosterone response to mild stress (Bourke et al., 2013). Mice treated prenatally with SSRIs displayed enhanced aggressive behaviors relative to vehicle-treated controls in a number of studies (Kiryanova & Dyck, 2014; Svirsky et al., 2015; Coleman et al., 1999). SSRIs have been shown to both decrease levels of circulating corticosterone and lead to impaired negative feedback regulation of corticosterone in rats (Gobinath et al., 2016; Pawluski et al., 2012). Route of administration, dose and time of testing influence the outcome. That noted, mice exposed to a similar treatment regimen

to the one that impaired HPA axis negative feedback regulation (Gobinath et al., 2016), demonstrated reduction in aggressive behavior at adulthood relative to control (Yu et al., 2014).

Exposure to addictive substances and medicines *in utero* can lead to both hypo and hyperactivity of the HPA axis later in life. Whether alterations in HPA axis activity in response to challenge represent general hypo- or hyper-function of the axis remains unknown. Drug-induced alteration of HPA axis function is associated with both increase and decreases in aggressive behavior depending on the drug in question. Effects of drug exposure during adolescence, on the other hand, render a more coherent picture. Across drug classes, evidence, though scant, indicates that adolescent exposure leads to enhanced HPA axis response to stressors, as well as enhanced aggression.

6. Discussion

We have reviewed the existing literature to assess the potential presence of a link between aberrations in the development of the HPA axis in a diversity of animal models and the emergence of aggression (summarized in Table 1.). The literature described is generated from genetically-selected and inbred strains of rodents, as well as on the effects of developmental exposure to stress or drugs of abuse. A major drawback in establishing any firm conclusion is the lack of systematic studies including equivalent manipulations (e.g., timing and duration of treatments) and common protocols for the measurement of the HPA axis and aggressive behaviors.

Thus, although a general unifying picture cannot be extracted from the reviewed data, there are certain commonalities that ought to be emphasized. We found several examples suggesting that aberrations towards abnormally low or abnormally high HPA axis functionality taking place during development are associated to increased aggression, frequently characterized by pathological features. Thus, the reviewed literature suggests the existence of a U-shape function between developmental HPA axis reactivity and the emergence of aggressive phenotypes (Figure 1). Note, however, that the U-shaped function presented here is naturally speculative, since the majority of models outlined have assessed HPA axis (re)activity and aggression in two groups only. It is thus important for future research to perform experiments taking into account an intermediate group. Of the studies that considered three groups, the HAB/LAB rat lines have come closest to supporting the hypothesized U-shape. In that case, both of the selected lines showed enhanced aggression relative to non-selected controls, and also demonstrated high and low HPA axis reactivity, respectively (Beiderbeck et al., 2012; Neumann et al., 2005, 2010). However, crucial information regarding the relative level of HPA axis reactivity in the control group has not been so far reported.

Therefore, the currently available data can only partially support our hypothesis, and further experiments considering three experimental groups are warranted.

Other data from the animal literature, not reviewed here, show that the direct manipulation of glucocorticoids at adulthood, leading to both abnormally low (Haller et al., 2004; Haller et al., 2001) or high (Haller et al., 1997; Kruk et al., 2004) glucocorticoid levels can lead to pathological aggression. This is found alongside alterations in the activity of brain regions and circuits implicated in the control of aggression (Haller, 2014a, 2014b). However, a critical issue is whether aberrant HPA axis has a causal implication in the development of aggressive phenotypes.

Research linking both aspects from a developmental perspective is scarce and it is thus difficult to outline a comprehensive view that implies any particular link between extremes in HPA axis variation and features of pathological aggression. Indeed, the HPA axis is not a single unit and various outcomes may arise from a unique modification in the system. For example, a decrease in corticosterone production may lead to differential behavioral outcomes whether it is associated with a hypersensitivity to a regulator of aggression or in a negative feedback of the systems. Discrepancies between studies and outcomes, in addition to the already mentioned differences in protocols and species, may arise from the inappropriately focal picture observable using single-point analyses of HPA axis function employed by many studies in the field. Traditionally, in line with the 'hypoarousal theory' of violence (Raine, 1996), blunted activation of the stress systems has been proposed to be particularly associated with symptoms of psychopathy. However, enhanced HPA axis reactivity was also related to pathological aggression in several rodent models (e.g., post-weaning social isolation; lines bred for high anxiety, and lines bred for maintenance of wildness), potentially mimicking emotional-impulsive types of aggression. Importantly, recent evidence in humans suggests that, even within individuals high in psychopathic traits, there might be subtypes presenting not only blunted, but also high HPA responses to stress (Johnson et al., 2015).

A key question arising from this review is what are the neurobiological mechanisms that could mediate the negative impact of developmental deviations in HPA axis activity on social behaviors. Although addressing this question is beyond the scope of the present review (for more information, see Sandi and Haller, 2015) and a precise answer will require further studies, existing evidence indicates that abnormal glucocorticoid levels during key developmental periods can have detrimental effects on brain structure and function (Jacobson and Sapolsky, 1991; Feldman and Weidenfeld, 1998; Matthews, 2000; Welberg et al., 2000; Seckl, 2004; Eiland and Romeo, 2013), including changes in brain regions involved in both the

regulation of the HPA axis and aggression (e.g. amygdala, prefrontal cortex, and hypothalamus) (Haller, 2004; Haller, 2014a; Biro et al., 2016). Additionally, neuromodulators that are critically implicated in aggression – e.g., serotonin (5-HT) – may also be affected by differential HPA axis development (Seckl, 2004).

It is important to note that various experimental results summarized in this review show some inconsistencies and their interpretation must be taken with great care. For example, the effects of stress highly depend on the developmental stage at the time of stress, and this may not be directly comparable between species (Matthews, 2000; Lupien et al., 2009). Some species give birth to immature young animals (e.g., rats and mice) while others deliver mature young ones (e.g., guinea pigs and primates). Immature young animals continue to display considerable higher rates of neuronal development after birth (Sapolsky and Meaney, 1986) and exhibit a higher glucocorticoid receptor sensitivity than the young of species with substantial rates of maturity at birth (Claman, 1972). In addition, it is important to note that the "stress hypo-responsive period" displayed by rats on the two weeks following birth has been interpreted from as an adaptation to enable proper brain development (Sapolsky & Meaney, 1986; Schmidt et al., 2005).

We should also note that critical differences in the ontogeny of aggression between the two rodent species reviewed here, namely rats and mice, may influence the conclusions drawn from the reviewed literature. For example, as summarized above, mice and rats exposed to maternal separation were found to display opposite patterns of aggression in the context of similar HPA axis reactivity (Boccia & Pedersen, 2001; Hohmann et al., 2013; Parfitt et al., 2004; Tsuda et al., 2011; Veenema et al., 2006; Veenema & Neumann, 2009). In particular, we know that these two species differ in their engagement in social play. Thus, rats engage heavily in play-fighting during the juvenile period (Pellis and McKenna, 1995) and, when deprived of such play experience they show aberrant social behaviors at adulthood, from hyper-defensiveness and failure to display appropriate submissive behavior, to exaggerated aggression (Potegal & Einon, 1989; Vanderschuren et al., 1997). These observations led to the hypothesis that engagement in social play was critical to the development of appropriate social behaviors (Vanderschuren et al. 1997, Pellis & Pellis 1998). However, as compared to rats, the social play repertoire of mice is impoverished (Pellis & Pasztor, 1999; Pellis & Pellis, 1998; Terranova et al., 1998). Accordingly, the social development, including aggressiveness, of these two species may not follow the same developmental pattern. Given that HPA axis activity relating to social play has been implicated in the effective learning of social interaction patterns

(Achterberg et al., 2014), elevated corticosterone levels during early life might influence the way in which play and aggressive behaviors are embedded differentially in these two species.

Additionally, the nature and duration of stressors given in different studies could also be critical in determining differences in aggression. It has been shown that various stressors, and other environmental challenges, do not elicit the same glucocorticoid secretion in rodents (Koolhaas et al., 2011) and that the quality of the stressor might also shape (or prime) future stress responses (Branchi et al., 2013). Additionally, the results of stress may be altered by housing conditions early in life. For example, it was shown that socially-enriched environments, while being stressful due to the inherent increase in social interactions, may actually be protective against stress and favor stronger cognitive abilities (D'Andrea et al., 2007; Huzard et al., 2015). It is thus important to take factors such as this into account in order to compare models but data remain too disparate to be able to draw clear conclusions from additional factors.

Furthermore, we should also note that one limitation with animal studies is the difficulty to clearly differentiate reactive and proactive types of aggression. Although various studies have reported abnormal forms of aggressive behaviors in rodents, it remains difficult to distinguish whether the motivation to aggress. As previously described (Haller, 2014a), "aggression is not a unitary phenomenon" and can be divided is various subtypes. It is often suggested that hypo-reactive (hypoaroused, "cold") individuals perform proactive aggression whereas hyper-reactive (hyperaroused, "hot") individuals display reactive aggression (Blair, 2001; Caramaschi, 2008a; Haller, 2014a; Provençal et al., 2015). Subdivision of aggression likely involves a complex brain network. One may suggest that distinct components are taking place in the emergence of aggressive behaviors: the onset of an aggressive bout, the intensity (low or highly aggressive), the nature of the outcome (normal or abnormal), and the type/context (reactive or proactive). The neural pathways responsible for such components might be distinct but interconnected, giving rise to the broad panel of aggressive responses reported in the literature. The different components of aggression could be altered independently by developmental changes. However, at present there is no systematic analysis of those different criteria allowing a precise description of the variations induced by stress at different developmental stages. Finally, the U-shape model may not only applicable to "aggressiveness" as a whole but to the different components of aggression, leading to a multi-dimensional model comprising multiple outcomes, as observed in the diversity of aggressive behaviors described in the literature.

A further limitation regards the difficulty in assessing whether the findings of studies using male animals generalize to females. The neurobiology underlying aggressive behavior, in terms of the downstream effects of signaling molecules, as well as in neuroanatomy, shows sexual dimorphism (Haller, 2014a). Additionally, the influence of the HPA axis on female aggression is little studied, an issue more deeply entrenched with regard to the developmental aspect under review here. From the available evidence, the relationship in females between altered HPA axis activity during development and later aggressiveness appears to align with the findings observed in males. For example, in rat lines originally bred for variation in anxiety-like behavior (HAB/LAB: Liebsch et al., 1998), female HAB rats showed enhanced aggressiveness. This was observed both in lactating and virgin females (Bosch & Neumann, 2010; de Jong et al., 2014). Though no differences in basal levels or in stress-induced levels of HPA axis activity were observed, the aggressive HAB line females showed blunted HPA axis responsiveness to an injection of CRH (Neumann et al., 1998). Additionally, in rats selectively-bred for aggressiveness toward humans ("wild" vs. "tame"), female wild rats were more aggressive than tame rats, and showed enhanced levels of corticosterone under basal conditions (Albert et al., 2008). This alignment also holds with regard to some developmental stress models. Indeed, peripubertally stressed female rats were found to show enhanced maternal aggression, as well as enhanced aggression prior to mating (Cordero et al., 2013). No differences in circulating corticosterone were found but increased basal vasopressin was observed (Cordero et al., 2013). In contrast, maternally-separated female rats showed reduced maternal aggression in the context of lower basal levels of corticosterone and enhanced responsiveness following stress (Aisa et al., 2008; Boccia & Pedersen, 2001; Koe et al., 2014; Slotten et al., 2006). Taken together these studies indicate that females showing alterations in HPA axis activity during development may display dysfunctional aggression later in life. Moreover, from the examples described above, it appears that female rats in which the HPA axis is under enhanced feedback-mediated inhibitory control may be more aggressive (Bosch & Neumann, 2010; de Jong et al., 2014; Neumann et al., 1998; Albert et al., 2008; Cordero et al., 2013; Boccia & Pedersen, 2001; Slotten et al., 2006; Koe et al., 2014; Aisa et al., 2008). These findings support a link between HPA axis hypo-responsiveness and enhanced aggression in females, in line with observations reviewed above in males. However, owing to the paucity of studies in females, we cannot draw any conclusion regarding the potential existence of a U-shape for them.

In conclusion, the reviewed evidence highlights a complex, but potentially critical link between developmental HPA axis activity and the development of social disturbances. In order to capture the causal link between these two elements in a time- and dose-controlled manner, future animal experiments should aim toward specific manipulation of HPA axis function using a variety of experimental approaches.

This research is much needed, given the suggestion that children with callous-unemotional traits might benefit from interventions capable of normalizing their blunted cortisol levels (van Goozen et al., 2007). Importantly, the data reviewed here indicate that genetic differences or other factors might critically affect neurodevelopmental trajectories influenced by aberrations –either high or low- in HPA axis function.

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Figure and Table legends

Figure 1. U-shaped relationship between HPA axis functioning and aggressive behavior. HPA axis activity driven toward either hypo- or hyper-function is linked to exaggerated emission of aggression, often with abnormal features. Species, substrain and developmental stage also influence this relationship.

Table 1. Summary of literature describing the link between HPA axis function and aggressive behavior. ↑: represents an increase; ↓: a decrease; = not different; ?: not known; SHR: Spontaneously Hypertensive Rat; WKY: Wistar-Kyoto rat; F344: Fischer 344 rat; SD: Sprague-Dawley rat.

Highlights :

- Analysis of link between genetic and environmental models of HPA axis aberration and aggression
- Suggestion of U-shaped relationship between HPA axis activity and aggressive phenotypes
- Developmental timepoint, species and substrain critically influence link between HPA axis aberrations and development of aggression