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Adolescence and the Ontogeny of the Hormonal Stress Response in Male and Female Rats and Mice

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Highlights

- Adolescence is associated with many neuroendocrine changes
- Adolescents show stress-induced changes in ACTH and corticosterone secretion
- These changes are dependent on stressor type, experience, and sex

Abstract

Adolescent development is marked by many changes in neuroendocrine function, resulting in both immediate and long-term influences on an individual's physiology and behavior. Stress-induced hormonal responses are one such change, with adolescent animals often showing different patterns of hormonal reactivity following

a stressor compared with adults. This review will describe the unique ways in which adolescent animals respond to a variety of stressors and how these adolescent-related changes in hormonal responsiveness can be further modified by the sex and previous experience of the individual. Potential central and peripheral mechanisms that contribute to these developmental shifts in stress reactivity are also discussed. Finally, the short- and long-term programming effects of chronic stress exposure during adolescence on later adult hormonal responsiveness are also examined. Though far from a clear understanding of the neurobehavioral consequences of these adolescent-related shifts in stress reactivity, continued study of developmental changes in stress-induced hormonal responses may shed light on the increased vulnerability to physical and psychological dysfunctions that often accompany a stressful adolescence.

Keywords: adolescence, adrenal, HPA axis, hypothalamus, pituitary, puberty, stressor

1. Introduction

Adolescence is a developmental stage that can be broadly defined as the transition of an individual from being dependent on a caregiver to a state of self-reliance. It is also marked by substantial changes in an individual's physiological and neurobehavioral function, which in part permits the individual to navigate this transition successfully. Though adolescence is clearly associated with many physical and cognitive gains, it can also be a period of heightened vulnerability to myriad dysfunctions, such as the onset of mood disorders and other psychopathologies

(Andersen, 2003; Dahl and Gunnar, 2009; Lee et al., 2014). The factors that mediate this increased vulnerability are uncertain, but exposure to chronically challenging, stressful environments during adolescence appears to contribute to the likelihood of developing a psychological disorder (Grant et al., 2003; Grant et al., 2004; Tottenham and Galvan, in press; Turner and Lloyd, 2004). The mechanisms through which exposure to stressors lead to these dysfunctions are not well understood, however many studies have reported that the manner in which pre- and post-adolescent animals respond to stressors can be quite different (McCormick et al., 2015; McCormick and Mathews, 2007; McCormick and Mathews, 2010; McCormick et al., 2010; Romeo, 2010a, b, 2013). This review will concentrate on the adolescent development of the hormonal stress response and the neuroendocrine mediators that may underlie these maturational changes in stress reactivity. Furthermore, this review will focus largely on data derived from studies utilizing non-human animal subjects, namely rats and mice. Prior to beginning the discussion on adolescent-related shifts in stress-induced hormonal responses, we will first describe the mechanics of the hypothalamic-pituitary-adrenal (HPA) axis, the primary neuroendocrine axis that controls the release of stress-related hormones.

2. Hypothalamic-Pituitary-Adrenal (HPA) Axis

In reaction to experiencing a stressor, be it physical or psychological, animals mount hormonal responses in an attempt to restore homeostasis. One major “stress response” is that mediated by the HPA axis. The secretion of hormones by this axis is driven by a cascade of signals starting with the production and release of corticotropin-

releasing hormone (CRH) from the medial parvocellular division of the paraventricular nucleus of hypothalamus (PVN). CRH is released into the hypophyseal portal system, which in turn initiates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. It should be noted that in addition to CRH, vasopressin (AVP), also secreted by the PVN, can synergize with CRH to further potentiate the ACTH response (Antoni, 1993; Rivier and Vale, 1983). ACTH then stimulates the secretion of the glucocorticoids (i.e., cortisol in primates and corticosterone in many rodent species) from the adrenal cortex. Similar to other neuroendocrine axes, the output of the HPA axis is modulated via negative feedback, such that stress-induced increases in glucocorticoid levels activate inhibitory pathways that reduce further hypothalamic CRH and AVP release and ACTH secretion from the pituitary gland (Herman and Cullinan, 1997; Sapolsky et al., 2000; ***Figure 1***).

The glucocorticoids execute their actions via the mineralocorticoid and glucocorticoid receptors (MR and GR, respectively). These receptors are found in relatively high concentrations throughout the neural–pituitary network that influences HPA reactivity and limbic and cortical regions involved in various aspects of emotionality, cognitive processes, and executive functions (de Kloet et al., 2005; McEwen, 2005; McEwen et al., 1968, 1969; Sapolsky et al., 2000). As a high affinity receptor for the glucocorticoids, the MR is typically saturated at basal glucocorticoid levels, while the lower affinity GR is usually occupied only when glucocorticoid concentrations are elevated (de Kloet et al., 1998). Thus, when glucocorticoid levels rise in response to stressors, the effects in the nervous system are primarily mediated by the GR (de Kloet et al., 1998).

In the short-term, the interaction between these hormones and their receptors mediate many beneficial effects, such as mobilization of needed energy stores, reduction of inflammation, and enhanced immune activity and memory formation (Dhabhar, 2009; McEwen, 2007; Roozendaal, 2000; Sapolsky et al., 2000). This active process is termed allostasis and it is thought to promote adaptation in response to challenging, stressful events (Karatsoreos and McEwen, 2011; McEwen and Stellar, 1993; McEwen and Wingfield, 2010). However, if an organism experiences prolonged and repeated exposure to these stress-related hormones, negative effects on physiological and neurobehavioral function may emerge, including altered metabolism, suppressed immunity, cognitive deficits, and psychiatric disorders (Herbert et al., 2006; McEwen, 2003, 2004, 2005; McEwen and Stellar, 1993; Sapolsky, 1999; van Praag, 2004). This process is termed allostatic load and can be thought of as the cumulative "wear and tear" on the organism under chronically stressful conditions (Karatsoreos and McEwen, 2011; McEwen and Stellar, 1993; McEwen and Wingfield, 2010). Therefore, factors modulating the responsiveness of the HPA axis and the balance between adaptive and maladaptive responses could have significant and widespread consequences for the organism.

3. Adolescent Development of HPA Stress Reactivity

An animal's developmental stage can profoundly influence its physiological, neurobiological, and behavioral response to a stressor. The adolescent stage of development and its role in modulating stress reactivity have been gaining increasing attention (McCormick and Mathews, 2007; McCormick and Mathews, 2010; McCormick

et al., 2010; Romeo, 2010a, b, 2013). The first experimental evidence regarding changes in stress-induced hormonal reactivity before and after adolescent maturation was that described by Goldman, Winget, Hollingshead, and Levine in 1973 (Goldman et al., 1973). In their seminal paper, the authors reported that pre-adolescent (25-day-old) and adult (65-day-old) male rats exposed to either hypoxia (i.e. ether inhalation,) or intermittent foot shock showed significantly different patterns of plasma corticosterone release. Specifically, the pre-adolescent rats exhibited a more prolonged corticosterone response than did the adults (Goldman et al., 1973). Other laboratories later replicated and extended these results, showing that pre-adolescent male and female rats and mice (25-30 days of age) exposed to other physical and/or psychological stressors, such as short bouts of hypoxia, hypoglycemia, or 30 min of restrain stress, exhibited plasma ACTH and corticosterone responses that lasted twice as long as those observed in adults ($\geq$ 65 days of age; Foilb et al., 2011; Romeo et al., 2013; Romeo et al., 2006b; Romeo et al., 2004a; Romeo et al., 2004b; Spinedi et al., 1997; Vazquez and Akil, 1993; ***Figure 2***). These prolonged responses in pre-adolescent animals are for both total and bioavailable corticosterone, as plasma levels of corticosterone binding globulin (CBG) is similar in pre-adolescent and adult animals (Romeo et al., 2006a). Overall, the data from these lines of research would suggest that, in response to numerous stressors, pre-adolescent animals experience significantly longer exposures to ACTH and bioavailable corticosterone compared with adults.

Further extrapolating from the observation that animals show differential stress-induced hormonal responses before and after adolescent development, a series of experiments in rats were conducted to assess at what point during adolescence the

transformation to an adult-like pattern of stress reactivity occurs. It was found that the adult-like ACTH stress response from the pituitary develops during the later stages of adolescence (50-60 days of age), while the corticosterone response from the adrenal gland changes earlier (30-40 days of age; Foilb et al., 2011). These results indicate that shifts in hormonal stress responses occur throughout adolescence and that each gland along this neuroendocrine axis displays a unique developmental trajectory.

It is important to note that not all stressors lead to protracted ACTH and corticosterone responses in peri-adolescent animals. For instance, brief exposures to a novel environment (Goldman et al., 1973) or social isolation (Hodges et al., 2014) result in similar corticosterone responses in pre-, mid- and post-adolescent rats. Furthermore, some stressors, such as exposure to lipopolysaccharide (Girard-Joyal et al., 2015; Goble et al., 2011) or placement in the open arm of an elevated plus maze (McCormick et al., 2008) evoke lesser ACTH and/or corticosterone secretion in pre- and mid-adolescent male rats and female mice compared to adults (***Figure 3***). Therefore, these data highlight the importance of stressor type in instigating age-dependent changes in hormonal stress reactivity. These data also suggest that differential rates of maturation may occur along the discrete neural pathways that mediate activation of the HPA axis in response to different types of challenges, including social, physical, or immunological stressors.

4. Experience and Adolescent Development Interact to Shape HPA Stress Reactivity

Another factor responsible for significant shifts in stress-induced hormonal responses is prior experience with stress. In adults, animals repeatedly exposed to the same stressor (i.e., homotypic stressor) often exhibit reduced hormonal reactivity to that stressor (Bhatnagar et al., 2002). Notably, however, when pre-adolescent animals are exposed to a homotypic stressor, such as repeated bouts of restraint stress, no habituation in their hormonal responsiveness is observed (Doremus-Fitzwater et al., 2009; Lui et al., 2012; Romeo et al., 2006a; ***Figure 4***). It should be noted that both adolescent and adult rats exhibit habituation to reoccurring episodes of social isolation, indicating that habituation depends on the stressor encountered (Hodges and McCormick, 2015). On the other hand, when adults are repeatedly exposed to homotypic stressor and then exposed to a novel stressor (i.e., heterotypic stressor) they often exhibit sensitized hormonal responses compared with adults exposed to the novel stressor alone (Bhatnagar and Dallman, 1998). Pre-adolescent males also exhibited a sensitized hormonal response following exposure to a heterotypic stressor (Lui et al., 2012). Similar to the prolonged response observed in pre-adolescent rats following a single, acute stress exposure, it was also found that pre-adolescent males recovered to baseline more slowly after termination of the heterotypic stressor than did adults (Lui et al., 2012; ***Figure 4***). These data indicate that age and experience can interact to shape HPA reactivity.

Whether there is a physiological advantage to having greater and more protracted hormonal responses during adolescence is unknown. Given that

corticosterone plays a major role in metabolism and energy mobilization (Pecoraro et al., 2006; Sapolsky et al., 2000), it is possible that these heightened stress-induced corticosterone responses permit greater energy usage to help compensate for the increased metabolic demand of adolescence. Though no direct experimental evidence supports this presumption, it has been shown that pre-adolescent rats exposed to restraint stress not only have greater corticosterone release than adults but also show significantly higher plasma glucose levels (Romeo et al., 2007a). Other evidence, however, indicates that the adolescent's ability to mobilize greater energy stores under chronic stress conditions is not sufficient to meet the metabolic needs for growth and development during puberty. More specifically, when adults are exposed to three weeks of chronic restraint stress, they exhibit a 10% reduction in body weight compared with a 30% decrease in adolescents (Eiland et al., 2012). Clearly, additional data are needed to better understand the energetic ramifications and implications of the differential responses exhibited by adolescent and adult animals following stress and specifically how these responses may meet the distinctive physiological and behavioral demands of adolescence.

5. Neuroendocrine Mechanisms that may Mediate Adolescent-Related Shifts in HPA Stress Reactivity

The mechanisms that mediate adolescent- and experience-related changes in hormonal stress reactivity remain unclear. So far, they appear to involve both the central activation and negative feedback phases of the HPA response as well as potential shifts in the sensitivity of the peripheral glands of the HPA axis to their

respective secretagogues. The next two sections will discuss research implicating neural inputs converging on the PVN and their role in mediating adolescent changes in stress reactivity, followed by a discussion of the research highlighting the contribution of the pituitary and adrenal glands to these changes.

5.1 Neural Basis: Activity of the Paraventricular Nucleus and Negative Feedback

The PVN in general, and the parvocellular region specifically, receives afferent inputs from various limbic, hypothalamic and brainstem nuclei that modulate its activity in reaction to stressors (Herman et al., 2003; Ulrich-Lai and Herman, 2009). In particular, the PVN receives direct projections from the anteroventral/fusiform area of the bed nucleus of the stria terminalis (aBST; (Dong et al., 2001) and from the nucleus of the solitary tract (NTS;(Cunningham et al., 1990; Cunningham and Sawchenko, 1988), which activate the PVN through their glutamatergic and adrenergic inputs, respectively, during exposure to stressors (Choi et al., 2008; Choi et al., 2007; Crestani et al., 2013; Dong et al., 2001; Plotsky, 1987; Plotsky et al., 1989; Szafarczyk et al., 1987; ***Figure 5***). These areas in turn receive projections from limbic and sensory inputs that relay information about the nature of the stressor (Herman et al., 2003; Ulrich-Lai and Herman, 2009). Conversely, many hypothalamic and limbic areas send direct GABAergic, inhibitory signals to the PVN, including the medial preoptic (MPO; Cullinan et al., 1996; Sawchenko and Swanson, 1983; Viau and Meaney, 1996), posterior BST (pBST; Choi et al., 2007; Dong and Swanson, 2004; Sawchenko and Swanson, 1983), ventrolateral portion of the dorsomedial nucleus (DMN; Boudaba et al., 1996;

Sawchenko and Swanson, 1983), and the area immediately adjacent to and surrounding the PVN (peri-PVN; Roland and Sawchenko, 1993; Ziegler and Herman, 2000; ***Figure 5***). These inhibitory regions are integral for tonic inhibition of the axis as well as decreased HPA activity during the negative feedback phase of the stress response (Cullinan et al., 2008; Herman et al., 2003; Herman et al., 2004; Ulrich-Lai and Herman, 2009).

The anatomical studies above have been conducted largely on adults but almost no research has studied the potential differences in the afferent connectivity of the PVN in adolescent animals or the relative contribution of excitatory versus inhibitory signals in mediating the siginificant age and experential modifications in stress-induced hormonal responsiveness. We do know, however, that the PVN of pre-adolescent males shows significantly greater activation, as indexed by FOS immunohistochemistry (i.e., a marker of cellular activity), compared with that of adults following exposure to either single or repeated bouts of restraint stress (Lui et al., 2012; Romeo et al., 2006a; ***Figures 6 and 7***). Given that the PVN is a relatively heterogeneous nucleus, comprised of diverse cell groups expressing a variety of neurochemicals (Swanson and Sawchenko, 1983), further studies have been conducted to probe the phenotype of these differentially activated cells. Specifically, using triple-labeled immunofluorescence histochemistry to quantify the cell number and relative co-labeling of FOS, CRH, and AVP positive cells, it was found that a significantly larger proportion of CRH, but not AVP, cells were activated in the pre-adolescent PVN compared with that of the adult in response to either single or repeated bouts of restraint stress (Romeo et al., 2006a; ***Figure 8***). These results indicate that CRH neurons of the PVN are one neural locus

that is likely involved in age- and experience-dependent changes in HPA hormonal reactivity.

It is important to note that PVN morphology (e.g., volume, cell number, cell size), number of CRH and AVP cells, and the number of anterior pituitary projecting neurosecretory neurons are comparable before and after adolescent development (Romeo et al., 2006a; Romeo et al., 2007b). Moreover, although basal CRH mRNA in the PVN is slightly higher in pre-adolescent versus adult rats (Romeo et al., 2007b), stress results in elevated CRH expression at both ages (McCormick et al., 2007; Romeo et al., 2007b; Viau et al., 2005). Thus, instead of gross changes in PVN morphology, hormonal content, or efferent projections to the anterior pituitary, these data collectively suggest that the significant changes in stress reactivity, at least in response to restraint stress, in part reflect maturational changes in signaling processes within the PVN and/or the excitatory and inhibitory afferents to this nucleus. Future studies will need to directly assess these possibilities.

In addition to potential changes in the drive to the HPA axis via activation of the PVN, the greater and more prolonged stress-induced hormonal responses observed in adolescent animals may also be mediated by changes in negative feedback. In the original study by Goldman and colleagues (Goldman et al., 1973) showing adolescent-related differences in hormonal reactivity, it was noted that the synthetic glucocorticoid dexamethasone was less effective at blunting a stress-induced (ether inhalation) corticosterone response in pre-adolescents compared with adult male rats, indicating reduced negative feedback in pre-adolescent animals. Despite these reported adolescent-related changes in negative feedback on the HPA axis, there appears to be

very little difference in the levels of GRs in the neural-pituitary network that mediate corticosterone-dependent negative feedback in rats or mice (Dziedzic et al., 2014; Romeo et al., 2008; Romeo et al., 2013; Vazquez, 1998). These data would suggest that any alterations in negative feedback prior to adolescence are likely mediated by factor(s) other than changes in GR levels. However, it cannot be ruled out that adolescent-related changes in function of the GR (or MR) are involved in these shifts in negative feedback, so future studies should examine potential age-dependent changes in receptor trafficking and/or levels of receptor co-factors, mechanisms that have been previously implicated in modulating GR-mediated negative feedback (Meijer et al., 2006; Mizoguchi et al., 2009; Spiga and Lightman, 2009).

5.2 Altered Sensitivity to Secretagogues of the Hypothalamus and Pituitary

Along with changes in the central nervous system that may impact the adolescent maturation of HPA reactivity, it is possible that shifts in the responsiveness of the pituitary to CRH and AVP and of the adrenal to ACTH could contribute to these adolescent changes in stress-induced ACTH and corticosterone levels. Though no data currently exist in the context of potential adolescent-related changes in the sensitivity of the pituitary to CRH and/or AVP, one study reported a decreased adrenal sensitivity to ACTH in male rats as they transitioned into adulthood. Specifically, at lower levels of exogenously supplied ACTH, pre-adolescent males had significantly higher corticosterone concentrations than adults (Romeo et al., 2014). It was also reported that, following restraint stress, the adrenal glands of pre-adolescents compared with adult males showed greater expression of melanocortin receptor accessory protein

(MRAP), a molecule that chaperones the melanocortin 2 receptor (i.e., the receptor for ACTH) to the cell surface (Cooray and Clark, 2011; Hinkle and Sebag, 2009; Webb and Clark, 2010). Though these data support a role for greater adrenal sensitivity to ACTH in contributing to the protracted stress-induced corticosterone response in pre-adolescent animals, ACTH is not the only factor responsible for corticosterone secretion following stress. For example, splanchnic nerve innervation of the adrenal glands can influence corticosterone release, independent of ACTH (Engeland, 1998). Thus, additional *in vitro* studies would help to more directly determine both the time course and dose response of secretagogue-evoked ACTH and corticosterone release from the pituitary and adrenal, respectively, and whether age or previous stress experience significantly affect these outcomes.

Though not specifically related to sensitivity, studies have also indicated that the pre-adolescent adrenal gland shows both greater basal and stress-induced increases in corticosterone content compared to those levels measured in adults (Foilb et al., 2011). Therefore, it would appear that a combination of increased sensitivity to ACTH and greater corticosterone content of the adrenal gland may underlie the prolonged corticosterone response observed in pre-adolescent animals following stress exposure. It is currently unknown whether there are age-dependent differences in ACTH concentrations in the pituitary gland, but future studies will need to investigate this possibility as well as changes in pro-opiomelanocortin levels, the precursor to ACTH.

6. Adolescent Stress Exposure and the Programming of the HPA Axis

To this point, the data reviewed above have described the unique ways in which the peri-adolescent stress-induced HPA response differs from that of adults. This section will now shift that focus to examine the effects that stress exposure during adolescence has on later stress reactivity in adulthood. Similar to the results discussed above, these long-term influences of adolescent stress exposure on adult responsiveness are highly dependent on the type of stressor(s) experienced as well as the stage of adolescent development during which the experience occurred. Moreover, these effects are often different in males and females, suggesting sex differences in the resilience of or vulnerability to the enduring influences of stress on adult HPA function.

6.1 Chronic Variable Stress (CVS)

One of the first experiments to assess long-term effects of chronic stress exposure during adolescence on later stress reactivity in rats was conducted by Isgor and colleagues in 2004 (Isgor et al., 2004). In this study, male rats were exposed to chronic variable physical or social stress for four weeks starting at 28 days of age. For the physical stress regimen, animals underwent either one or two randomly assigned stressors per day, including forced swim, restraint, loud noise, cold exposure, and ether inhalation. The social stressors were administered with the same frequency, and included isolation, exposure to novel environments, crowding, litter shifting, and subordination. Either twenty-four hours or three weeks after these chronic variable stress paradigms were terminated (i.e., at either 57 or 77 days of age), animals were placed in the open arm of an elevated plus maze for 15 min to evoke a corticosterone response. It was found that the animals exposed to either physical or social stress

showed greater hormonal reactivity than controls did 24 h after termination of the variable stress exposure, while only the animals exposed to the physical stress regimen continued to exhibit this enhanced responsiveness 3 weeks after the chronic stress had ceased (Isgor et al., 2004). These data highlight at least two important points: first, that chronic stress exposure during adolescence can lead to both short- and long-term changes in later hormonal stress reactivity; and second, physical stressors may leave a longer lasting impact on future HPA function than social stressors.

Many studies have since followed, using various stress paradigms over longer or shorter stretches of adolescent development and assessing HPA function in adulthood. For example, CVS in males for 14 days during early adolescence (35-48 days of age), late adolescence (50-63 days of age), or adulthood (80-93 days of age) resulted in heightened hormonal stress reactivity in all three age ranges after 10 min of forced swim stress. However, when females were exposed to 14 days of CVS during late adolescence (45-58 days of age) they showed no changes in hormonal reactivity following 10 min of forced swim immediately after cessation of CVS, but did display blunted ACTH and corticosterone responses following forced swim when tested later in adulthood (101 days of age; Wulsin et al., 2016). Similar results were found in females when CVS was administered earlier in adolescence (37-49 days of age), but stress-induced hypo-responsiveness was noted both immediately after CVS had been terminated as well as weeks later in adulthood (Bourke and Neigh, 2011). This reduced HPA function was also noted in adult females, but not males, in the context of decreased basal, resting corticosterone levels following either CVS applied between 37-

44 days of age (Taylor et al., 2013) or repeated restraint stress between 32-50 days of age (Barha et al., 2011).

6.2 Social Stress

In addition to CVS paradigms, which often include components of physical stress, like hypoxia, immobilization, and exposure to cold, there are also many social stress regimens, which consist largely of psychological stressors like isolation and/or repeated changing of cage mates (McCormick et al., 2015). Though social stressors during adolescence generally lead to milder effects on HPA responsiveness in adulthood than those caused by CVS or repeated physical stressors, social stressors can still cause changes in HPA function. For example, an experiment using 1 hour daily bouts of social isolation during early- to mid-adolescence (30-45 days of age) or adulthood (70-85 days of age) found that both adolescent and adult male rats show habituated corticosterone responses to the repeated isolation (Hodges and McCormick, 2015). However, only adolescent males repeatedly exposed to isolation displayed increased hormonal reactivity following pairing with an unfamiliar cage mate, an effect not seen in the adults (Hodges and McCormick, 2015). The effects of repeated isolation do not appear to be long lasting, as males and females exposed to these daily bouts of isolation from 30-45 days of age show no difference from controls in their novelty-evoked corticosterone response when tested at 70 days of age in adulthood (McCormick et al., 2008). It should be noted, however, that if the isolation during adolescence is more extreme, then there can be long-term effects on HPA responsiveness. For instance, adolescent male and female rats that are socially

isolated for three weeks (from 30-50 days of age) show sex-specific changes in HPA reactivity when tested in adulthood (70 days of age). Specifically, adult males that had previously undergone isolation during adolescence exhibit a reduced corticosterone response to restraint stress compared to socially raised controls, while adult females previously isolated show enhanced restraint-induced corticosterone responses compared to control females (Weintraub et al., 2010). Interestingly, these effects on hormonal reactivity were only noted in plasma corticosterone levels, and not ACTH levels, suggesting that these long-term and sex-specific effects of social isolation during adolescence were mediated by changes in adrenal sensitivity rather than hypothalamic or pituitary function (Weintraub et al., 2010). It is important to note that a social isolation experiment conducted on adolescent male mice lead to somewhat different results, in that social isolation spanning adolescent development (from 21-70 days age) resulted in reduced basal corticosterone levels, but heightened corticosterone reactivity to a novel environment, compared with controls (Ros-Simo and Valverde, 2012). Though the length of time spent in social isolation differed between these rat and mouse studies, these data underscore the fact that effects of adolescent social stressors on adult HPA function may show some species specificity.

Social instability stress during adolescence can also cause changes in HPA function in adulthood. More specifically, studies in both male and female mice show that twice weekly cage mate changes for seven weeks across adolescent development (from 21-70 days of age) result in elevated basal corticosterone levels in the morning compared with non-socially disturbed controls (Schmidt et al., 2010; Schmidt et al., 2007; Sterlemann et al., 2008). Interestingly though, the reverse pattern in basal

corticosterone secretion is observed during the night, at least in males, who showed reduced basal levels compared with controls (Sterlemann et al., 2008). Therefore, social instability experienced during adolescence can lead to altered HPA function, but the direction of these alterations depends on the time of day of sampling, and potentially the sex of the subject.

6.3 Predator Odor Stress

Another stress paradigm commonly used to probe programming effects of adolescent stress exposure on later HPA function is repeated presentation of predator odors, including cat odor and trimethylthiazoline (TMT), a chemical designed to mimic the odor of fox feces. While repeated exposure to TMT during early adolescence in male and female rats does not appear to influence HPA reactivity when tested later in adulthood (Toledo-Rodriguez and Sandi, 2007, 2011), a single exposure to soiled cat litter at 28 days of age results in suppressed basal corticosterone levels in those same animals at 60 days of age (Bazak et al., 2009). Moreover, repeated exposures to cat odor during mid-adolescence (between 40-48 days of age) lead to habituation of corticosterone responses to later presentations of cat odor in female, but not male rats (Wright et al., 2008). Though it is currently unknown if these effects carry into later adulthood, these data do suggest that stressors, which activate innate fear pathways (Figueiredo et al., 2003), can influence the development of HPA function in a sex-specific manner.

6.4 Exogenous Corticosterone Administration

Instead of exposing rodents to a stressor(s), experimenters can administer exogenous corticosterone during pubertal and adolescent maturation to directly assess the impact of corticosterone exposure on shaping HPA axis function in adulthood. For instance, it was found that male rats repeatedly treated with corticosterone during early- and mid-adolescence at 28, 29, 30, 34, 36, 40, and 42 days of age showed significantly lower levels of plasma corticosterone in adulthood following a 15 min exposure to novelty compared to control-treated rats (Veenit et al., 2013). Similarly, adolescent rats administered corticosterone through their drinking water from days 30-45 showed suppressed plasma corticosterone responses compared to vehicle controls after 20min of a forced swim stressor (Waters and McCormick, 2011). This later finding, however, may be due to the negative feedback actions of elevated corticosterone levels in the treated animals, as they were exposed to the stressor only 48h after the chronic treatment with oral corticosterone had been ended. Overall though, these data suggest that long-term changes in HPA function following adolescent stress exposure may be mediated, in part, by the direct actions of corticosterone on the adolescent brain.

6.5 Summary

Taken together, the data reviewed above indicate short- and/or long-term effects of chronic stress during adolescence on later HPA reactivity that can be both stressor- and sex-dependent. Though many questions remain unanswered, such as the mechanism through which these changes in HPA reactivity are mediated, the transient, permanent, or even transgenerational nature of these effects (Saavedra-Rodriguez and

Feig, 2013; Zaidan and Gaisler-Salomon, 2015), as well as the implications of altered HPA function on physiological and behavioral potentials in adulthood, these studies highlight the lasting trace that stressful experiences can leave on an individual. Furthermore, it will be important to understand whether these changes in HPA function are different when the chronic stressors are experienced either during adolescence, when neural circuits and endocrine systems are in flux, or during adulthood, when neurobehavioral maturation is largely complete. For instance, we have previously argued that the impact of stressors may be greater on the adolescent compared to the adult nervous system due to the continued maturation of stress-sensitive limbic and cortical regions during adolescence (Eiland and Romeo, 2013; Romeo, in press).

7. Conclusions

In summary, the studies discussed above have focused on the unique changes in stress-induced hormonal responses that can occur during adolescence, as well as the influence on these changes that can depend on stressor type, previous experience, and sex of the individual. Though we are far from a complete mechanistic understanding of these adolescent-related changes in HPA function, there are clear contributions from both central and peripheral factors. Thus, it will be important to examine how each level of the axis contributes in distinct ways to these shifts in HPA reactivity. As we carry with us our experiences from one life stage to the next, we will need to consider the cumulative, synergistic, and interactive effects of stressors experienced during earlier sensitive and critical periods of development on programming adolescent stress reactivity, and whether these effects are ultimately

adaptive or maladaptive for the organism upon reaching adulthood. (see (Tottenham and Galvan, in press) in this issue). Finally, given both the short- and long-term effects of chronic stress exposure during adolescence on HPA function in adulthood, and the association between a stressful adolescence and later physiological and psychological dysfunctions (Andersen, 2003; Dahl and Gunnar, 2009; Grant et al., 2003; Grant et al., 2004; Lee et al., 2014; Turner and Lloyd, 2004), it will be imperative to further delineate the adverse neurobehavioral ramifications of chronic stress exposure during adolescence in basic animal models (Eiland and Romeo, 2013; McCormick and Green, 2013; McCormick and Mathews, 2010; McCormick et al., 2010; Sandi and Haller, 2015). Therefore, the valuable information we gain from the study of stress and adolescent HPA development will not only lead us to a better understanding of the parameters that affect the physical and mental health of adolescents, but also the well-being of the adults they will become.

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Figure Captions:

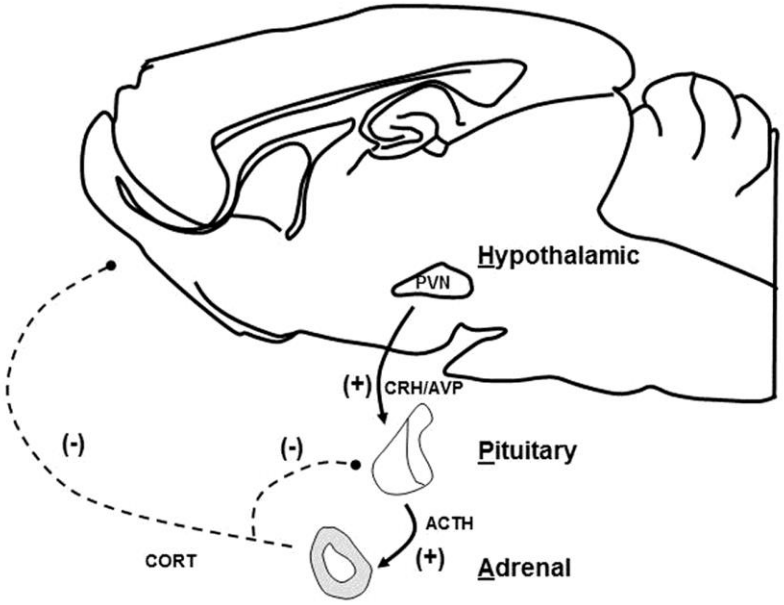

Figure 1. A schematic representation of the hypothalamic-pituitary-adrenal (HPA) axis. Solid lines with arrowheads = positive drive (+) of the secretagogues to each gland, while dashed lines with oval heads = the neural-pituitary target tissues that provide negative feedback (-). Abbreviations: ACTH, adrenocorticotropin hormone; AVP, arginine vasopressin; CORT, corticosterone; CRH, corticotropin-releasing hormone; PVN, paraventricular nucleus of the hypothalamus.

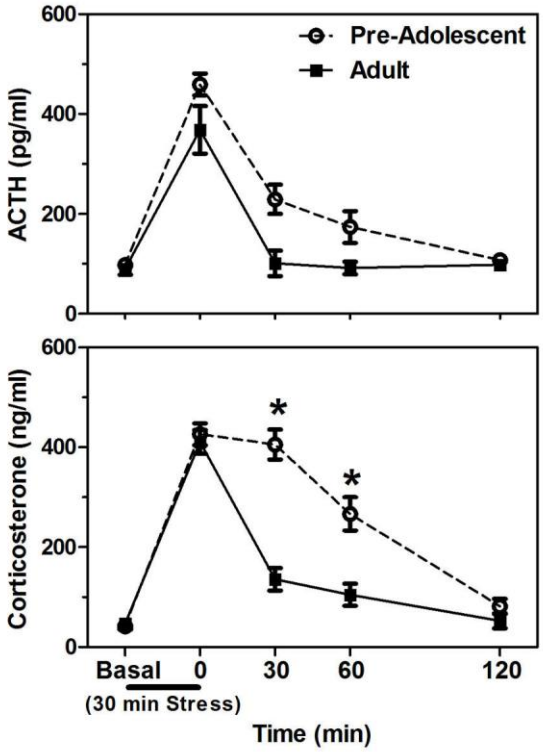

Figure 2. Plasma ACTH (top panel) and corticosterone (bottom panel) levels in pre-adolescent (28 days of age) and adult (77days of age) male rats before, during, and after a 30 min session of restraint (black bar under x-axis). Asterisks indicate a significant difference between the ages. Adapted from (Romeo et al., 2004a).

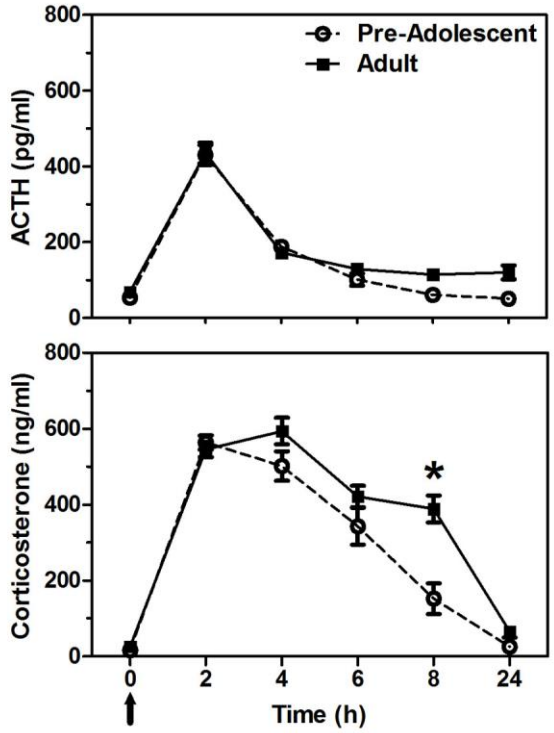

Figure 3. Plasma ACTH (top panel) and corticosterone (bottom panel) levels in pre-adolescent (28 days of age) or adult (68 days of age) male rats before (Time 0h) or 2, 4, 6, 8, and 24 h following a LPS injection (0.1 mg/kg, i.p.). Arrowhead indicates the LPS treatment. Asterisk indicates a significant difference between the ages. Adapted from (Goble et al., 2011).

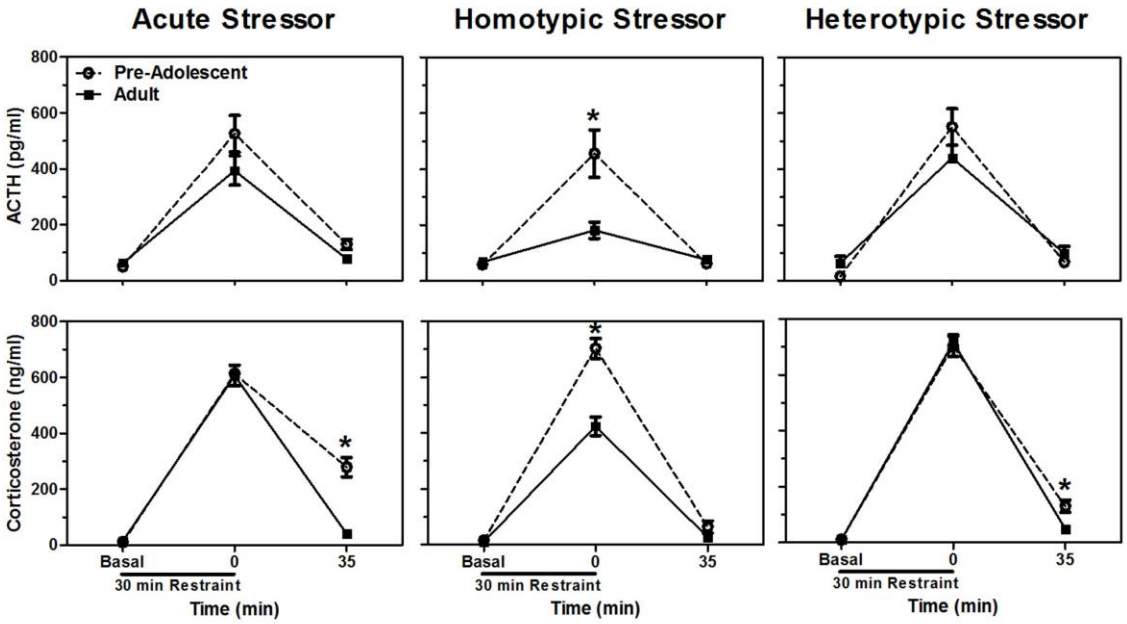

Figure 4. Plasma ACTH (top panels) and corticosterone (bottom panels) in pre-adolescent (30 days of age) and adult (77 days of age) male rats exposed to a single, acute stress (left panels), homotypic stress (middle panels), or heterotypic stress (right panels). Asterisks indicate a significant difference between the ages. Adapted from (Lui et al., 2012).

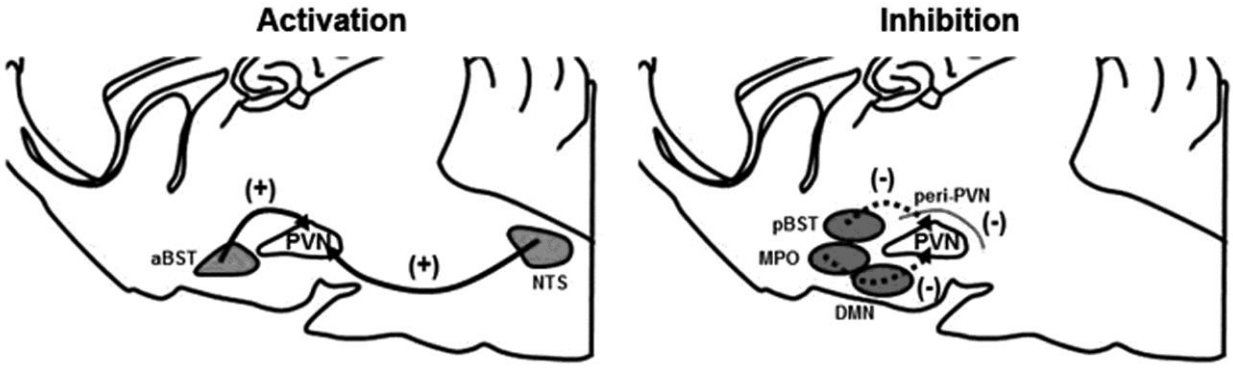

Figure 5. A schematic representation of the direct excitatory (left panel) and inhibitory (right panel) inputs to the PVN that modulate stress-induced HPA responses. Though these pathways have been well mapped out in adults, it is unknown if these PVN afferents show adolescent-related changes in structural or functional connectivity. Abbreviations: aBST, anteroventral/fusiform area of the bed nucleus of the stria terminalis; DMN, ventrolateral portion of the dorsmedial nucleus; MPO, medial preoptic nucleus; NTS, nucleus of the solitary tract; pBST, posterior bed nucleus of the stria terminalis; peri-PVN, area immediately adjacent to and surrounding the paraventricular nucleus; PVN, paraventricular nucleus of the hypothalamus.

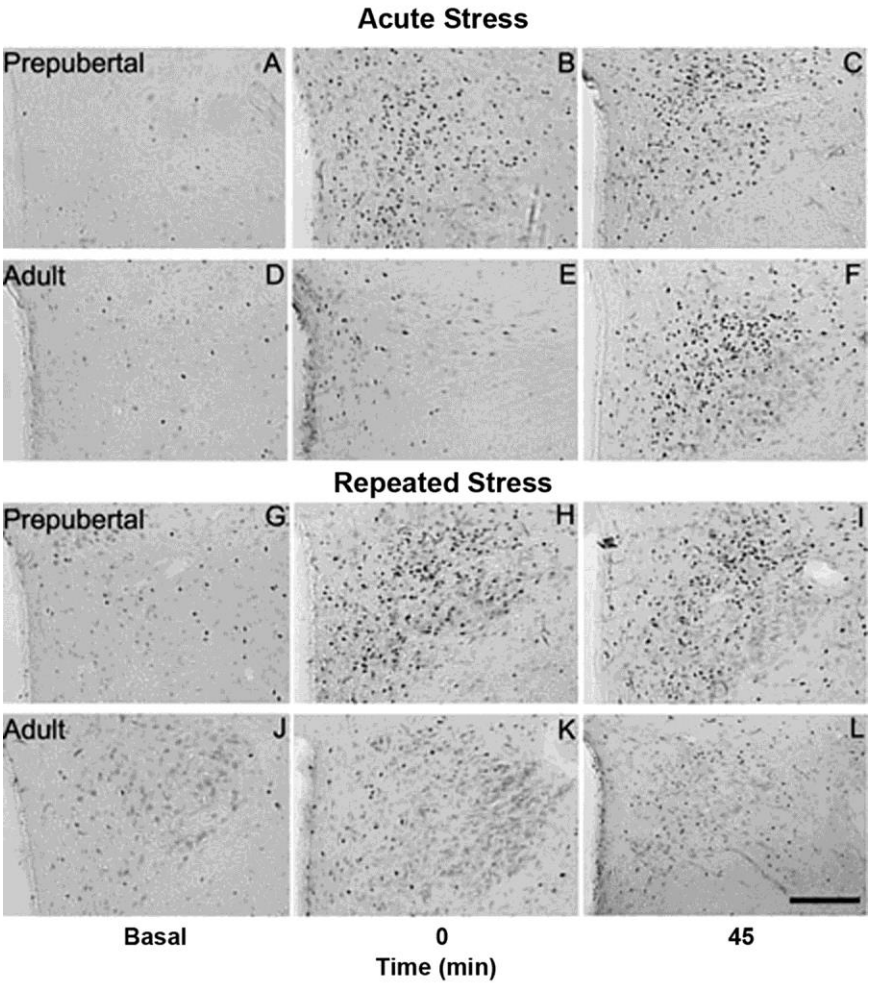

Figure 6. FOS-immunoreactive cells in the PVN of pre-adolescent (28 days of age) and adult (77 days of age) male rats following either a single, acute 30 min session of restraint (A-C and D-F, respectively) or daily 30 min session of restraint for one week (repeated stress; G-I and J-L, respectively). Scale bar, 150µm. Adapted from (Romeo et al., 2006a).

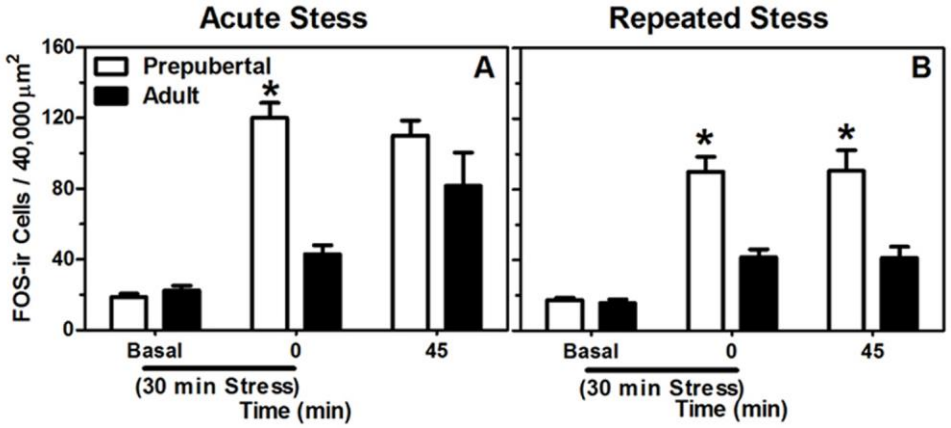

Figure 7. FOS-immunoreactive cells / 40,000mm2 in the PVN of pre-adolescent (28 days of age) and adult (77 days of age) male rats following either a single, acute 30 min session of restraint (A) or a daily 30 min session of restraint for one week (repeated stress; B). Asterisks indicate a significant difference between the ages. Adapted from (Romeo et al., 2006a).

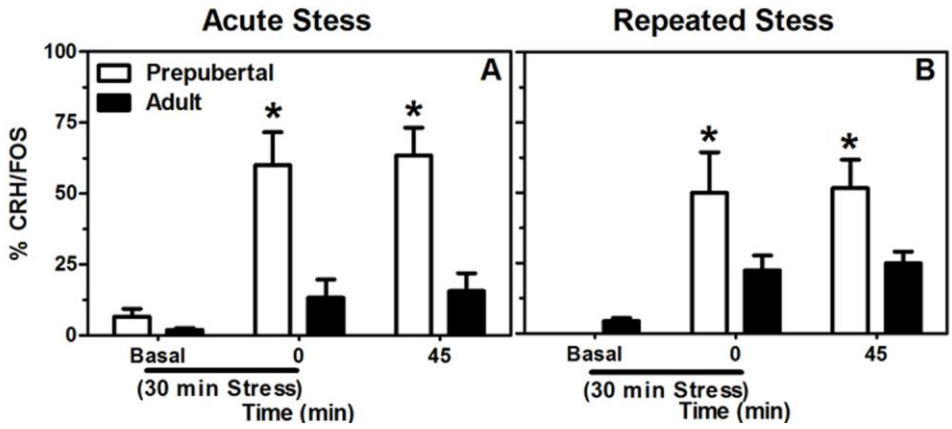

Figure 8. Percent CRH and FOS double-labeled cells in the PVN of pre-adolescent (28 days of age) and adult (77 days of age) male rats following either a single, acute 30 min session of restraint (A) or a daily 30 min session of restraint for one week (repeated stress; B). Asterisks indicate a significant difference between the ages. Adapted from (Romeo et al., 2006a).