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The Metamorphosis of Adolescent Hormonal Stress Reactivity: A Focus on Animal Models

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Abstract

As adolescents transition from childhood to adulthood, many physiological and neurobehavioral changes occur. Shifts in neuroendocrine function are one such change, including the hormonal systems that respond to stressors. This review will focus on these hormonal changes, with a particular emphasis on the pubertal and adolescent maturation of the hypothalamic-pituitary-adrenal axis. Furthermore, this review will concentrate on studies using animal models, as these model systems have contributed a great deal to our mechanistic understanding of how factors such as sex and experience with stress shape hormonal reactivity during development. Continued study of the maturation of stress reactivity will undoubtedly shed much needed light on the stress-related vulnerabilities often associated with adolescence as well as providing us with possible strategies to mitigate these vulnerabilities. This area of research may lead to discoveries that enhance the well-being of adolescents, and ultimately providing them with greater opportunities to mature into healthy adults.

Keywords

Adolescence; Developmental; HPA Axis; Maturation; Puberty

1. Adolescence and Stress-Related Vulnerabilities: A Clinical Context

Adolescence represents a unique stage in an individual's physiological and neurobehavioral maturation, associated with many developmental gains, such as somatic growth and increased cognitive abilities (Luna et al., 2004; Best and Miller, 2010; Ellison et al., 2012). Unfortunately, however, adolescence is also marked by a variety of psychological and physiological developmental vulnerabilities and dysfunctions, including mood disorders, drug abuse, and obesity (Kessler et al., 2007; Paus et al., 2008; Lee et al., 2014; Ogden et al., 2016; Peiper et al., 2016; Jordan and Andersen, 2017), the genetic, epigenetic, and environmental mediators of which are not completely understood.

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A number of studies have noted significant changes in hormonal stress reactivity during adolescence in both human and non-human males and females (Dahl and Gunnar, 2009; Gunnar et al., 2009; Romeo, 2013; McCormick et al., 2016; Romeo et al., 2016). In general, it has been noted that exposure to a variety of stressors lead to greater or more prolonged hormonal responses in adolescents compared to adults. Given the role of stress and stress-related hormones in psychological and physiological vulnerabilities in adulthood (de Kloet et al., 2005; Peters et al., in press), this developmental change in stress reactivity has been posited to be a contributing factor to the increased vulnerabilities noted during adolescence (Turner and Lloyd, 2004; Spear, 2009; Tottenham and Galvan, 2016; Romeo, 2017).

The purpose of this review is to describe adolescence-related changes in hormonal stress responses and the neuroendocrine mechanisms that might contribute to these developmental shifts in reactivity. This review will concentrate on experiments that have used non-human animals, mainly rats and mice, as the majority of studies that have contributed to our mechanistic understanding of adolescent development of hormonal stress reactivity has been conducted on these tractable model systems. Though this review will address general questions about adolescent maturation and stress responsiveness, readers interested specifically in human research are referred to a number of comprehensive reviews published previously on this topic (Guerry and Hastings, 2011; Doom and Gunnar, 2013; Hostinar and Gunnar, 2013; Hostinar et al., 2014; Marceau et al., 2015).

2. Hormonal Stress Response of the HPA Axis

Following exposure to a stressor, be it physiological and/or psychological, hormonal responses are activated. One such canonical hormonal response is that mediated by hypothalamic-pituitary-adrenal (HPA) axis. Specifically, stress-induced activation of neurosecretory cells in the parvocellular portion of the paraventricular nucleus (PVN) lead to the release of neuropeptides, such as corticotrophin-releasing hormone (CRH) and vasopressin (AVP), into the hypophyseal portal system. These neuropeptides then stimulate the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which in turn, leads the release of glucocorticoids (i.e., cortisol in primates and corticosterone in many rodent species) from the adrenal cortex (Herman et al., 2003). As glucocorticoid levels rise, they mediate numerous physiological and neurobehavioral processes that help an individual return to a homeostatic state and cope in the presence of perturbations, an active process termed allostasis (Karatsoreos and McEwen, 2011).

The increase in glucocorticoid levels also feeds back on the pituitary gland and numerous cortical, hypothalamic and limbic brain regions to reduce the further release of ACTH, CRH, and AVP, thus terminating the hormonal response (Herman and Cullinan, 1997; Sapolsky et al., 2000; Herman et al., 2003; Ulrich-Lai and Herman, 2009). The termination of the HPA response and its return to baseline are critical, as this permits the axis to respond to future challenges to homeostasis, as well as limit the body's exposure to these stress-related hormones. In fact, unnecessary, sustained exposure to these hormones can lead to allostatic load, which under conditions of repeated and persistent activation may result in a maladaptive state of allostatic overload (Karatsoreos and McEwen, 2011). Thus, the hormonal response mediated by the HPA axis allows an individual to overcome and adapt to

stressors, but the activation and recovery of the response are important facets to its effective and efficient function. It appears that during adolescent development, both the activation and recovery of the HPA response change as the axis matures into its adult-like state.

3. Studying Puberty and Adolescence and Stress Reactivity in Animal Models

The data reviewed in this manuscript are derived mainly from studies using animal models, such as rats and mice. As the HPA hormonal response is highly conserved across mammals, it is possible to use these tractable models to gain a deeper understanding of the mechanisms that contribute to developmental changes in HPA function and reactivity. However, prior to reviewing these data, it might be useful to operationally define some specific terms, briefly argue for the validity of these animal models, and identify approximate age spans often used in this type of animal research.

Though sometimes used interchangeably, puberty and adolescence are specific terms with different meanings. In particular, puberty is a discreet physiological event, driven by the hypothalamic-pituitary-gonadal (HPG) axis that culminates in attaining reproductive function and the ability to sire and care for offspring, while adolescence, broadly defined, is a developmental transition from dependence on caregivers to independence from caregivers. Given these types of broad definitions, it is rather clear that many mammals, including rats and mice, would have pubertal and adolescent stages of development. For instance, pubertal onset in rodents is marked by physiological, somatic, and endocrinology changes similar to that observed in humans, such as gonadal maturation and sustained increases in gonadal hormone secretion (Ojeda and Urbanski, 1994). Neurobehavioral changes that occur across species during adolescent maturation also strengthen the face validity of the comparison between rodents and human and non-human primates. The increase in motivated behaviors, such as mating and aggressive behaviors, and the decrease in social behaviors, such as play, are a few examples (Spear, 2000; Romeo et al., 2002; Pellis and Pellis, 2007). Moreover, neuromorphological changes in cortical and limbic brain regions in humans, including reduced frontal and increased hippocampal volumes (Goodman et al., 2014; Giedd et al., 2015), also show parallel changes during these developmental transitions in rats (Juraska and Willing, 2017). Thus, rodents can serve as valid models to investigate certain aspects of pubertal and adolescent development exhibited by primates, including humans.

Despite the similarities between these shifts in various physiological and neurobehavioral domains, the chronological age at which these changes occur can be vastly different between species. For instance, a conservative estimate for the onset of puberty to late adolescence/young adulthood in humans would be 10 and 18 years of age, respectively, while rats and mice may span 30 and 70 days of age. Moreover, the terms used to identify the specific peri-adolescence stage of development of experimental subjects can vary across experiments and usually are relatively arbitrary. In an attempt to provide consistency while reviewing this literature, this paper will parse out adolescent development in rodents as follows: 25–35 days of age as pre-adolescent; 36–50 days of age as mid-adolescent; 51–64 days of age as late-adolescent; and 65 days of age and older as adult (Figure 1). However, it is important to

note that the exact age ranges that encompass particular stages of pubertal, adolescent, or adult development in any species would have to take into consideration the specific physiological, neurobiological, or behavioral variable measured, as well as the sex of the subject, as these factors could require contracting or expanding these general timeframes (Juraska and Willing, 2017).

4. Adolescent Changes in HPA Stress Reactivity

4.1 Acute Stressors

Seymour Levine and colleagues conducted the initial set of experiments that first described adolescence-related changes in hormonal stress reactivity in 1973 (Goldman et al., 1973). Here, it was shown that pre-adolescent male rats displayed a significantly prolonged stress-induced adrenal corticosterone response compared to adults. More specifically, following either hypoxia or intermittent foot shock exposures, pre-adolescent animals displayed a plasma corticosterone response that lasted 30–45 min longer than that in adults (Goldman et al., 1973). Though there are subtle changes in corticosterone metabolism in rats during the first three weeks of life, the change in metabolism after 30 days of age is minimal (Schapiro et al., 1971). Therefore, this protracted response in pre-adolescent rats cannot be explained by mere age-dependent differences in the rate of corticosterone clearance/metabolism from circulation. It was later reported that stress-induced ACTH levels also show a significantly protracted response in pre-adolescent compared to adult male rats (Vazquez and Akil, 1993), indicating these changes are not limited to just the adrenocortical portion of HPA axis. Since these seminal publications, many laboratories have replicated and extended these results, using various stress paradigms, including restraint, hypoglycemia, and immune challenges (Romeo et al., 2016). These adolescent changes in hormonal stress reactivity have also been reported in males and females (Minhas et al., 2016), during both the circadian peak and nadir of HPA function (Romeo et al., 2006b), and in rats and mice (Spinedi et al., 1997; Romeo et al., 2013; Figure 2).

Given that these shifts in hormonal responsiveness occur during a relatively wide time window (i.e., 30–40 days), we conducted an experiment assessing stress-induced ACTH and corticosterone responses in male rats spanning pre-adolescent to adult stages of development. We found that these shifts in reactivity occur rather abruptly, such that ACTH responses assume their adult-like patterns between 50–60 days of age, while corticosterone responses shift between 30–40 days of age (Foillb et al., 2011). Thus, it appears that these changes in hormonal reactivity are not incremental during adolescence, and that the responses from the pituitary and adrenal glands have their own unique developmental trajectories (Figure 3). Furthermore, despite that influence of gonadal hormones on HPA reactivity in males and females (Viau, 2002), it is important to note these protracted responses in pre-adolescent compared adult animals appear to be independent of pubertal changes in testicular or ovarian hormones in both males and females (Romeo et al., 2004a; Romeo et al., 2004b).

Not all stressors in peri-adolescent animals lead to extended HPA responses. For instance, Levine and colleague's original paper reported that exposure to a novel environment resulted in similar corticosterone responses in pre-adolescent and adult rats (Goldman et al., 1973).

Moreover, social isolation leads to equivalent hormonal responses in adolescent and adult rats (Hodges et al., 2014). There are also stressors that evoked greater corticosterone responses in adult mice and rats compared to pre-adolescent animals, such as a lipopolysaccharide (LPS) immune stressor (Goble et al., 2011; Girard-Joyal et al., 2015). It should be noted, however, that LPS is able to stimulate adrenal corticosterone release even in the absence of hypothalamic or pituitary function (Suzuki et al., 1986; Elenkov et al., 1992), suggesting immune stressors might be operating in unique ways to modulate HPA responses compared to other physiological and psychological stressors. Regardless, these studies indicate that the type of stressor examined and the mechanism(s) through which they lead to hormone release are important factors when studying adolescent maturation of the HPA stress reactivity. Overall, however, it would appear that stressors with at least both psychological and physiological components, such as hypoxia, foot shock, or restraint, lead to greater and more prolonged ACTH and corticosterone responses in peri-adolescent males and females compared to adult.

4.2 Repeated and Chronic Stressors

Previous experience with a stressor can also modify the adolescence-related changes in hormonal stress reactivity. In adults, experiencing the same stressor (i.e., homotypic) in a recurring fashion will often lead to a habituated HPA response (Grissom and Bhatnagar, 2009). For instance, adults repeatedly exposed to restraint stress will exhibit a reduced peak ACTH and corticosterone response compared to adults exposed to restraint stress for the first time (Hauger et al., 1990; Lachuer et al., 1994). Pre-adolescent male and female rats do not show this habituated hormonal response, instead exposure to a homotypic stressor, like repeated restraint, leads to higher hormonal responses than those observed following the first exposure to the stressor (Romeo et al., 2006a; Doremus-Fitzwater et al., 2009; Lui et al., 2012; Figure 4). It is important to note that adolescent animals do habituate to some types of homotypic stress, such as reoccurring episodes of social isolation (Hodges and McCormick, 2015). Thus, similar to the stressor specificity issue raised in the previous section, the type of stressor, in addition to the developmental stage, can have a profound impact on any experience-dependent changes in the hormonal responsiveness.

Along with homotypic stressors, heterotypic stressors (i.e., repeated exposure to a homotypic stressor followed by a novel stressor) can also lead to alter hormonal reactivity, usually manifested as sensitized or facilitated responses. For example, adult male rats repeatedly exposed to a cold room (4°C) for four hours a day and then exposed to a 30 min of restraint show higher peak ACTH and corticosterone responses than adults only exposed to the 30 min session of restraint (Bhatnagar and Dallman, 1998). Similar to adults, pre-adolescent male rats also display augmented hormonal responses following heterotypic stress exposure (Lui et al., 2012), though pre-adolescent animal return to baseline corticosterone levels more slowly after termination of the heterotypic stressor than adults (Lui et al., 2012). It is currently unknown whether pre-adolescent females exhibit these types of hormonal changes to heterotypic stressors. Moreover, it is unclear how many exposures to a particular stressor it takes for these experience-dependent changes to occur in pre-adolescent animals or how long these responses remain following a homotypic or heterotypic stress experience in pre-adolescent animals. However, these experiments do

indicate that developmental stage, experience, and stressor type can interact to modify HPA hormonal reactivity.

4.3. Implications of Developmental changes in HPA Stress-Induced Hormonal Reactivity

We are far from a clear understanding of why pre-adolescent animals show these disparate hormonal responses compared to adults following a single or repeated exposure to a stressor. However, given the role of glucocorticoids in metabolic function and the partitioning of energy (Rohner-Jeanrenaud, 1999; Pecoraro et al., 2006), these shifts in hormonal reactivity might help meet the differential energetic demands likely imposed by stressors at these two diverse maturational states. It should be noted that chronic exposure to stress during adolescence in male rats results in greater weight loss than when the exposure occurs in adulthood (Eiland et al., 2012). Thus, these data suggest differential sensitivities to the metabolic impacts of stress before and after adolescence, perhaps favoring reproductive maturation over ponderal growth during the transition to adulthood. Yet, the experimental evidence that links these changes in hormonal stress reactivity to specific physiological or behavioral demands unique to adolescent animals are lacking. Further experiments are needed to clarify the reasons for these shifts in hormonal stress reactivity and the costs and benefits they impart on the developing individual.

One area of research with more clarity, however, is our understanding of some of the neurobehavioral sequelae of stress and stress-related hormone exposure during adolescence. For instance, there is a growing literature devoted to revealing the short- and long-term effects of stress exposure during adolescence on emotional behaviors and cognitive functions (reviewed in; McCormick et al., 2010; Green and McCormick, 2013; McCormick and Green, 2013; Burke et al., 2017; Tielbeek et al., in press). The influence of stress exposure during adolescence on neural structure and function is also gaining wider experimental attention (reviewed in; Eiland and Romeo, 2013; Tottenham and Galvan, 2016; Romeo, 2017). However, the direct role that changes in hormonal stress reactivity play in these stress-induced neurobehavioral modifications are uncertain. As noted above, further experiments are needed to address the consequences of these hormonal changes and their involvement in neurobehavioral function and dysfunctions during adolescence.

5. Central Mechanisms Mediating Changes in Stress-Induced HPA Reactivity during Adolescence

In the most general terms, the stress-induced HPA hormonal response has at least two relatively distinct stages: the activation/drive stage and the recovery/negative feedback stage. The activation/drive portion includes the stress-induced initiation of the hormonal response and its continuation until stressor termination. The recovery/negative feedback portion of the response spans the time between cessation of the stressor and the return to baseline levels of hormone secretion. The mechanisms that contribute to these stages of the HPA response overlap in time and the distinction is somewhat arbitrary. However, in an effort to structure the discussion of the neuroendocrine mechanisms thought to contribute to changes in hormonal stress reactivity during adolescence, the next two sections will use this simplified

dichotomy to describe potential mediators of altered drive and/or feedback on the adolescent compared to adult HPA axis.

5.1 Activation/Drive of the HPA Hormonal Response

As described in Section 2 (Hormonal Stress Response of the HPA Axis), the stress-induced HPA response is initiated by the activation of CRH-containing cells in the PVN. These CRH cells in the PVN receive direct excitatory inputs from the anteroventral/fusiform area of the bed nucleus of the stria terminalis (aBST; Dong et al., 2001) and the nucleus of the solitary tract (NTS; Cunningham and Sawchenko, 1988; Cunningham et al., 1990). These projections activate the PVN through their glutamatergic and noradrenergic inputs (Plotsky, 1987; Szafarczyk et al., 1987; Plotsky et al., 1989; Dong et al., 2001; Choi et al., 2007; Choi et al., 2008; Crestani et al., 2013). Therefore, it is possible that greater inputs from these PVN afferents mediate the prolonged hormonal reactivity noted in pre-adolescent animals, though neuroanatomical tract tracing data supporting this assertion are lacking.

We have conducted a series of studies examining the cellular activity of neurons in the PVN in pre-adolescent and adult animals before, during, and after exposure to a variety of stressors. Specifically, we have used FOS immunohistochemistry (IHC) to label metabolically active cells and measure stress-induced neural responses in males before and after adolescent development. We and others find a greater number of FOS-positive cells in the PVN of stressed pre-adolescent animals compared to adults in response to either a single (Viau et al., 2005; Romeo et al., 2006a; Lui et al., 2012) or repeated exposure to restraint stress (Romeo et al., 2006a; Lui et al., 2012; Figure 5). Moreover, we find these greater FOS responses happen within the CRH-containing cells, as a higher proportion of FOS and CRH double-labeled cells are found in the pre-adolescent than adult PVN (Romeo et al., 2006a; Figure 5). Despite these differences in stress-induced activation, the number of CRH-containing cells and the size of the cells in the PVN are similar before and after adolescent development (Romeo et al., 2006a; Romeo et al., 2007). Furthermore, the number of neurosecretory cells labeled in the PVN after a peripheral injection of the retrograde tracer Fluoro-Gold are similar in pre-adolescent and adult male rats (Romeo et al., 2007). Collectively, these data suggest that increased stress-induced neural activity, specifically among the CRH cells in the PVN, might be contributing to these greater hormonal responses prior to adolescence. Whether these differences in activation of CRH-containing cells in the PVN are observed in pre-adolescent and adult females after exposure to a stressor remain to be established.

The upstream mediator(s) of this greater stress-induced PVN activation are currently unknown. However, we have begun to assess the activity of nuclei that project directly and indirectly to the PVN. For instance, we have recently examined potential differences in the stress-induced activation of norepinephrine-containing A2 neurons in the NTS using double-labelling IHC for FOS and dopamine beta hydroxylase (DBH), the rate-limiting enzyme in norepinephrine production. Though we did find fewer DBH-positive cells in the A2 region of adult compared pre-adolescent males, the FOS response in these cells is similar at both ages (Pham et al., 2017). We have also reported similar FOS responses following stress in the central nucleus of the amygdala in pre- and post-pubertal males (Romeo et al., 2006a). We

are currently mapping potential differences in the activation of other PVN afferents known to stimulate CRH release, such as the aBST and the dorsomedial nucleus (DMN), as well as investigating their structural connectivity via track tracing methods in both males and females. Moreover, the contribution of age-related changes in PVN disinhibition should also be considered, as electrophysiological experiments conducted on hypothalamic slices of pre-adolescence male rats exposed to stress indicate changes in chloride homeostasis that result in GABAergic-mediated excitation of neurosecretory neurons in the PVN (Hewitt et al., 2009). These types of experiments, utilizing difference techniques from multiple levels of analysis, will undoubtedly help elucidate the role that excitatory inputs to the PVN, and excitation of the PVN neurosecretory cells themselves, play in these adolescent changes in hormonal stress reactivity.

5.2 Recovery/Negative Feedback of the HPA Hormonal Response

Similar to examining potential age-related differences in drive or activation of the HPA axis, we are also seeking out possible changes in the inhibitory tone and negative feedback on the HPA axis as mediators of the prolonged hormonal response in pre-compared to post-adolescent animals. For instance, many hypothalamic and limbic areas send GABAergic, inhibitory signals to the PVN, including the medial preoptic nucleus (Sawchenko and Swanson, 1983; Cullinan et al., 1996; Viau and Meaney, 1996), posterior BST (pBST; Sawchenko and Swanson, 1983; Dong and Swanson, 2004; Choi et al., 2007), and ventrolateral portion of the dorsomedial nucleus (DMN; Sawchenko and Swanson, 1983; Boudaba et al., 1996). These inhibitory regions, which also receive the cortical and hippocampal inputs important in glucocorticoid-dependent negative feedback on the HPA axis, are integral for reducing activity of the axis, particularly once a stressor has been encountered (Herman et al., 2003; Herman et al., 2004; Cullinan et al., 2008; Ulrich-Lai and Herman, 2009). Though it is still unclear whether projections from these nuclei change in quality or quantity throughout adolescence, studies are currently investigating their structural and functional connections to the PVN before and after adolescence. In the context of negative feedback, however, it has been reported that pre-adolescent male rats peripherally injected with dexamethasone, a synthetic glucocorticoid, 4h prior to ether inhalation stress demonstrated higher plasma corticosterone responses than similarly treated adults (Goldman et al., 1973). These data would suggest that glucocorticoid-dependent negative feedback on the pre-adolescent HPA axis is less than that observed in adults. However, in the same set of experiments, it was found that local hypothalamic implants of either hydrocortisone or dexamethasone equally reduced ether-induced plasma corticosterone levels in pre-adolescent and adult animals (Goldman et al., 1973). Thus, these implant studies in males would suggest that any change in negative feedback on the adolescent HPA axis might be subtle and its site of action likely outside of the hypothalamus.

Despite these potential changes in HPA negative feedback, studies have been unable to find significant age-related differences in glucocorticoid receptor (GR) levels in the pituitary and various brain nuclei responsible for glucocorticoid-dependent negative feedback. For instance, studies have shown that pre-adolescent male rats, and male and female mice, have similar levels of GR mRNA and protein in the pituitary, hippocampal formation, PVN, and medial prefrontal cortex (Vazquez, 1998; Romeo et al., 2008; Romeo et al., 2013; Dziedzic

et al., 2014; Green et al., 2016; Figure 6). Furthermore, exposure to stress has been shown to down-regulate GR expression similarly in the hippocampal formation of peri-adolescent and adult male rats (Romeo et al., 2008; Green et al., 2016). It would appear, therefore, that any change in glucocorticoid-dependent negative feedback before and after adolescence occurs in the absence of significant changes in GR levels in the neural-pituitary network that mediates negative feedback. It has been recently noted that translocation of hippocampal GR from the cytoplasm to the nucleus is greater in stressed pre-adolescent compared to adult male rats, which may be caused by the higher stress-induced corticosterone levels prior to adolescent development (Green et al., 2016). Thus, these data indicate that subtle adolescent-related changes exist in GR function in nuclei important in negative feedback, but the exact association between these differences in receptor trafficking and HPA regulation remain unknown.

Taken together, these data generally support the notion that changes in both activation of the HPA axis and negative feedback, play a role in these shifts in stress-induced hormonal responses during adolescence. Additional research will clearly be needed to more fully explain the specific mechanisms that contribute to these hormonal changes, such as the up-stream mediators of the greater stress-induced PVN activation and cellular substrates responsible for the reduced negative feedback prior to adolescent development.

6. Peripheral Mechanisms Mediating Changes in Stress-Induced HPA Reactivity during Adolescence

6.1 Pituitary Gland

In addition to the central components of the HPA axis influencing the adolescence-related shifts in hormonal stress reactivity, there also are changes in the peripheral components of the axis that may contribute these alterations in responsiveness. As mentioned above, the anterior pituitary gland is responsible for the CRH- and AVP-induced release of ACTH, which ultimately leads to the release of adrenal corticosterone (Herman and Cullinan, 1997). Despite the similar levels of ACTH circulating in the plasma under non-stressed, basal conditions, we have reported that the pituitary in pre-adolescent male and female rats contains a greater concentration of ACTH than the pituitary of adults (Patel and Romeo, 2016). It is currently unknown whether exogenous administration of CRH and/or AVP to pre-adolescent and adult animals results in differential ACTH responses or if levels of pro-opiomelanocortin (POMC), the precursor polypeptide to ACTH, change in the pituitary corticotrope cells during adolescent development. However, it is possible that the greater ACTH content in the pre-adolescent pituitary contributes to the greater stress-induced ACTH responses observed in rats prior to adolescence (Vazquez and Akil, 1993; Romeo et al., 2004a). Future studies will be needed to address these possibilities and investigate potential changes in corticotrope receptor levels that might mediate potential differential sensitivity to hypothalamic secretagogues (i.e., CRH and AVP receptors).

6.2 Adrenal Glands

Relative to the pituitary gland, we know considerably more about the effects of adolescence on the adrenals in the context of developing HPA function. First, similar to hormonal content

in the pituitary, the adrenals of pre-adolescent male and female rats have greater concentrations of corticosterone than adults (Foilb et al., 2011; Patel and Romeo, 2016). Furthermore, though exposure to stress leads to greater adrenal corticosterone production at both ages, stress-induced increases in adrenal corticosterone is greater in the pre-adolescent males (Foilb et al., 2011). These data suggest that the pre-adolescent adrenal might be more steroidogenic than the adult and/or the synthesizing enzymes responsible of the production of corticosterone, such as 11 β -hydroxylase, exhibit age-related changes in the adrenal cortex. Additional studies will be needed to elucidate these possibilities. Second, the pre-adolescent adrenals appear to be more sensitive to ACTH than those of the adult, such that similar adrenal corticosterone responses are observed at lower levels of ACTH exposure in pre- compared to post-adolescent males (Romeo et al., 2014; Figure 7). Finally, pre-adolescent males show greater stress-induced increases in adrenal melanocortin receptor accessory protein (MRAP) expression than adults (Romeo et al., 2014). As MRAP is a chaperone protein that helps insert the melanocortin 2 receptor into the cell membrane (Hinkle and Sebag, 2009), these data suggest increased adrenal sensitivity to ACTH prior to adolescence might be through a receptor trafficking mechanism leading to greater availability of ACTH receptors on the membrane of adrenocortical cells. Though we are currently conducting adrenal explant studies to directly assess dose response relationships between ACTH and corticosterone responses in pre-adolescent and adult male and female adrenals, these data lend support to the idea of adrenal involvement in the adolescent-related changes in HPA reactivity.

7. Adolescent-Related Changes in Other Stress-Induced Hormonal Responses

Along with changes in stress-induced secretion of ACTH from the pituitary and corticosterone from the adrenal gland, a variety of hormones from other glands, namely the gonads, show differential patterns of release depending on stress exposure and pubertal status. For instance, though stress results in elevated plasma progesterone levels in both pre-adolescent and adult male and female rats, these stress-induced increases are significantly higher in the pre-adolescent animals (Romeo et al., 2004a; Romeo et al., 2004b; Romeo et al., 2005; Green et al., 2016; Figure 8). It is important to note that this stress-induced progesterone response is likely both gonadal and adrenal in origin, as these responses persist, albeit to a lesser degree, in gonadectomized animals (Romeo et al., 2005). In males, it has been shown that gonadal testosterone levels are differentially affected by stress exposure, such that adults show stress-induced elevations of plasma testosterone levels, while pre-adolescent males display suppressed testosterone responses (Romeo et al., 2004a; Foilb et al., 2011; Green et al., 2016; Figure 8). Conversely, though plasma estradiol levels are higher in adult compared to pre-adolescent females, exposure to an acute stress does not alter these age-dependent differences in circulating estradiol levels (Romeo et al., 2004b; Hodes and Shors, 2005).

Similar to the implications of differential HPA reactivity, it is currently unclear what role these age-dependent hormonal responses play in physiological and neurobehavioral functions and dysfunctions. However, given the wide distribution of the receptors for these

hormones throughout the body and brain, a better appreciation of these stress-induced responses will be necessary to provide a greater holistic understanding of adolescence and developmental changes in stress-induced hormonal reactivity.

8. Conclusions

The studies reviewed above clearly indicated that adolescence is marked by significant changes in hormonal stress responses. These studies also show how these changes can be modified by additional variables, including sex, stress experience, and stressor type. Though far from a complete mechanistic understanding of what mediates these adolescent-related shifts in hormonal stress reactivity, continued examination of these neuroendocrine systems will undoubtedly shed further light on how pubertal and adolescent development shape physiological and neurobehavioral function in both the short- and long-term. It will also be important to examine how these changes in HPA reactivity map on to behavioral alterations that similarly show unique changes during adolescence, such as the reduced fear extinction that has been reported to occur transiently in both adolescent mice and humans (Pattwell et al., 2012). These changes might be coincidental, but they may also point to a more general set of stress-induced coping strategies employed by individuals that have to meet the specific demands of this developmental stage.

As alluded to throughout the review, many questions remain, and though progress has been made in some respects on how adolescence affects HPA function, numerous areas of research are still relatively under-explored. For instance, it is clear that stressors that occur during adolescence in rats, such as chronic variable stress (Isgor et al., 2004), social isolation (Weintraub et al., 2010; Hodges and McCormick, 2015), and repeated exposure to predator odor (Wright et al., 2008; Bazak et al., 2009), lead to changes in HPA function in adulthood, yet the mediators responsible for these alterations are unknown. Along these lines, a potentially rich avenue of research is the intersection between stress, development, and epigenetic modulation (Hunter et al., 2015). Given the long-term effects of stress during adolescence on later HPA function (McCormick and Mathews, 2007; Eiland and Romeo, 2013; McCormick and Green, 2013; McCormick et al., 2015), it would be interesting to explore the epigenetic landscape the results from a stressful adolescence and whether these epigenetic changes mediate these functional alterations (Hunter and McEwen, 2013). A greater appreciation of these factors could help in the development of behavioral or pharmacological interventions that might ameliorate earlier adversity. Building on these foundational animal studies, along with continued translational approaches, and greater insight into adolescent maturation of HPA function and hormonal stress reactivity in humans, this research will ultimately aid in our abilities to maximize gains and minimize vulnerabilities during this crucial stage of development.

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References

- Bazak N, Kozlovsky N, Kaplan Z, Matar M, Golan H, Zohar J, Richter-Levin G, Cohen H. Pre-pubertal stress exposure affects adult behavioral response in association with changes in circulating corticosterone and brain-derived neurotrophic factor. *Psychoneuroendocrinology*. 2009; 34:844–858. [PubMed: 19181453]
- Best JR, Miller PH. A developmental perspective on executive function. *Child Dev*. 2010; 81:1641–1660. [PubMed: 21077853]
- Bhatnagar S, Dallman M. Neuroanatomical basis for facilitation of hypothalamic-pituitary-adrenal responses to a novel stressor after chronic stress. *Neuroscience*. 1998; 84:1025–1039. [PubMed: 9578393]
- Boudaba C, Szabo K, Tasker JG. Physiological mapping of local inhibitory inputs to the hypothalamic paraventricular nucleus. *J Neurosci*. 1996; 16:7151–7160. [PubMed: 8929424]
- Burke AR, McCormick CM, Pellis SM, Lukkes JL. Impact of adolescent social experience on behavior and neural circuits implicated in mental health. *Neurosci Biobehav Rev*. 2017; 76:280–300. [PubMed: 28111268]
- Choi DC, Evanson NK, Furay AR, Ulrich-Lai YM, Ostrander MM, Herman JP. The anteroventral bed nucleus of the stria terminalis differentially regulates hypothalamic-pituitary-adrenocortical axis responses to acute and chronic stress. *Endocrinology*. 2008; 149:818–826. [PubMed: 18039788]
- Choi DC, Furay AR, Evanson NK, Ostrander MM, Ulrich-Lai YM, Herman JP. Bed nucleus of the stria terminalis subregions differentially regulate hypothalamic-pituitary-adrenal axis activity: implications for the integration of limbic inputs. *J Neurosci*. 2007; 27:2025–2034. [PubMed: 17314298]
- Crestani CC, Alves FHF, Gomes FV, Resstel LBM, Correa FMA, Herman JP. Mechanisms in the bed nucleus of the stria terminalis: involved in control of autonomic and neuroendocrine functions: a review. *Curr Neuropharmacol*. 2013; 11:141–159. [PubMed: 23997750]
- Cullinan WE, Helmreich DL, Watson SJ. Fos expression in forebrain afferents to the hypothalamic paraventricular nucleus following swim stress. *J Comp Neurol*. 1996; 368:88–99. [PubMed: 8725295]
- Cullinan WE, Ziegler DR, Herman JP. Functional role of local GABAergic influences on the HPA axis. *Brain Struct Funct*. 2008; 213.
- Cunningham ET, Bohn MC, Sawchenko PE. Organization of adrenergic inputs to the paraventricular and supraoptic nuclei of the hypothalamus in the rat. *J Comp Neurol*. 1990; 292:651–667. [PubMed: 2324319]
- Cunningham ET, Sawchenko PE. Anatomical specificity of noradrenergic inputs to the paraventricular and supraoptic nuclei of the rat hypothalamus. *J Comp Neurol*. 1988; 274:60–76. [PubMed: 2458397]
- Dahl RE, Gunnar MR. Heightened stress responsiveness and emotional reactivity during pubertal maturation: implications for psychopathology. *Dev Psychopathol*. 2009; 21:1–6. [PubMed: 19144219]
- de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. *Nat Rev Neurosci*. 2005; 6:463–475. [PubMed: 15891777]
- Dong HW, Petrovich GD, Watts AG, Swanson LW. Basic organization of projections from the oval and fusiform nuclei of the bed nuclei of the stria terminalis in adult rat brain. *J Comp Neurol*. 2001; 436:430–455. [PubMed: 11447588]
- Dong H-W, Swanson LW. Projections from bed nuclei of the stria terminalis, posterior divisions: implications for cerebral hemisphere regulation of defensive and reproductive behaviors. *J Comp Neurol*. 2004; 471:396–433. [PubMed: 15022261]
- Doom JR, Gunnar MR. Stress physiology and developmental psychopathology: past, present, and future. *Dev Psychopathol*. 2013; 25:1359–1373. [PubMed: 24342845]
- Doremus-Fitzwater TL, Varlinskaya EI, Spear LP. Social and non-social anxiety in adolescent and adult rats after repeated restraint. *Physiol Behav*. 2009; 97:484–494. [PubMed: 19345235]

- Dziedzic N, Ho A, Adabi B, Foilb AR, Romeo RD. Shifts in hormonal stress reactivity during adolescence are not associated with changes in glucocorticoid receptor levels in the brain and pituitary of male rats. *Dev Neurosci*. 2014; 36:261–268. [PubMed: 24903860]
- Eiland L, Ramroop J, Hill MN, Manely J, McEwen BS. Chronic juvenile stress produces corticolimbic dendritic architectural remodeling and modulates emotional behavior in male and female rats. *Psychoneuroendocrinology*. 2012; 37:39–47. [PubMed: 21658845]
- Eiland L, Romeo RD. Stress and the developing adolescent brain. *Neuroscience*. 2013; 249:162–171. [PubMed: 23123920]
- Elenkov I, Kovacs K, Kiss J, Bertok L, Vizi ES. Lipopolysaccharide is able to bypass corticotropin-releasing factor in affecting plasma ACTH and corticosterone levels: evidence from rats with lesions of the paraventricular nucleus. *J Endocrinol*. 1992; 133:231–236. [PubMed: 1319449]
- Ellison PT, Reiches MW, Shattuck-Faegre H, Breakey A, Konecna M, Urlacher S, Wobber V. Puberty as a life history transition. *Ann Hum Bio*. 2012; 39:352–360. [PubMed: 22716225]
- Foilb AR, Lui P, Romeo RD. The transformation of hormonal stress responses throughout puberty and adolescence. *J Endocrinol*. 2011; 210:391–398. [PubMed: 21746793]
- Giedd JN, Raznahan A, Alexander-Bloch A, Schmitt E, Gogtay N, Rapoport JL. Child psychiatry branch of the National Institute of Mental Health longitudinal structural magnetic resonance imaging study of human brain development. *Neuropsychopharmacology*. 2015; 40:43–49. [PubMed: 25195638]
- Girard-Joyal O, Faragher A, Bradley K, Kane K, Hrycyk L, Ismail N. Age and sex differences in c-Fos expression and serum corticosterone concentration following LPS treatment. *Neuroscience*. 2015; 305:293–301. [PubMed: 26117716]
- Goble KH, Bain ZA, Padow VA, Lui P, Klein ZA, Romeo RD. Pubertal-related changes in hypothalamic-pituitary-adrenal axis reactivity and cytokine secretion in response to an immunological stressor. *J Neuroendocrinol*. 2011; 23:129–135. [PubMed: 20969651]
- Goldman L, Winget C, Hollingshead GW, Levine S. Postweaning development of negative feedback in the pituitary-adrenal system of the rat. *Neuroendocrinology*. 1973; 12:199–211. [PubMed: 4353346]
- Goodman J, Marsh R, Peterson BS, Packard MG. Annual research review: the neurobehavioral development of multiple memory systems--implications for childhood and adolescent psychiatric disorders. *J Child Psychol Psychiatr*. 2014; 55:582–610.
- Green MR, McCormick CM. Effects of stressors in adolescence on learning and memory in rodent models. *Horm Behav*. 2013; 64:364–379. [PubMed: 23998678]
- Green MR, Nottrodt RE, Simone JJ, McCormick CM. Glucocorticoid receptor translocation and expression of relevant genes in the hippocampus of adolescent and adult male rats. *Psychoneuroendocrinology*. 2016; 73:32–41. [PubMed: 27448526]
- Grissom N, Bhatnagar S. Habituation to repeated stress: get used to it. *Neurobiol Learn Mem*. 2009; 92:215–224. [PubMed: 18667167]
- Guerry JD, Hastings PD. In search of HPA axis dysregulation in child and adolescent depression. *Clin Child Family Psychol Rev*. 2011; 14:135–160.
- Gunnar MR, Wewerka S, Frenn K, Long JD, Griggs C. Developmental changes in hypothalamus-pituitary-adrenal activity over the transition to adolescence: normative changes and associations with puberty. *Dev Psychopathol*. 2009; 21:69–85. [PubMed: 19144223]
- Hauger RL, Lorang M, Irwin M, Aguilera G. CRF receptor regulation and sensitization of ACTH responses to acute ether stress during chronic intermittent immobilization stress. *Brain Res*. 1990; 532:34–40. [PubMed: 2178035]
- Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trend Neurosci*. 1997; 20:78–84. [PubMed: 9023876]
- Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostander MM, Choi DC, Cullinan WE. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamic-pituitary-adrenocortical responsiveness. *Front Neuroendocrinol*. 2003; 24:151–180. [PubMed: 14596810]
- Herman JP, Mueller NK, Figueiredo HF. Role of GABA and glutamate circuitry in hypothalamo-pituitary-adrenocortical stress integration. *Ann NY Acad Sci*. 2004; 1018:35–45. [PubMed: 15240350]

- Hewitt SA, Wamsteeker JI, Kurz EU, Bains JS. Altered chloride homeostasis removes synaptic inhibitory constraint of the stress axis. *Nat Neurosci.* 2009; 12:438–443. [PubMed: 19252497]
- Hinkle PM, Sebag JA. Structure and function of the melanocortin2 receptor accessory protein (MRAP). *Mol Cell Endocrinol.* 2009; 300:25–31. [PubMed: 19028547]
- Hodes GE, Shors TJ. Distinctive stress effects on learning during puberty. *Horm Behav.* 2005; 48:163–171. [PubMed: 15885691]
- Hodges TE, Green MR, Simone JJ, McCormick CM. Effects of social context on endocrine function and Zif268 expression in response to an acute stressor in adolescent and adult rats. *Int J Dev Neurosci.* 2014; 35:25–34. [PubMed: 24613747]
- Hodges TE, McCormick CM. Adolescent and adult male rats habituate to repeated isolation, but only adolescents sensitize to partner familiarity. *Horm Behav.* 2015; 69:16–30. [PubMed: 25510393]
- Hostinar CE, Gunnar MR. Future directions in the study of social relationships as regulators of the HPA axis across development. *J Clin Child Adol Psychol.* 2013; 42:564–575.
- Hostinar CE, Sullivan RM, Gunnar MR. Psychological mechanisms underlying the social buffering of the hypothalamic-pituitary-adrenocortical axis: a review of animal models and human studies across development. *Psychol Bull.* 2014; 140:256–282. [PubMed: 23607429]
- Hunter RG, Gagnidze K, McEwen BS, Pfaff DW. Stress and the dynamic genome: steroids, epigenetics, and the transposome. *Proc Natl Acad Sci USA.* 2015; 112. [PubMed: 25535392]
- Hunter RG, McEwen BS. Stress and anxiety across the lifespan: structural plasticity and epigenetic regulation. *Epigenomics.* 2013; 5:177–194. [PubMed: 23566095]
- Isgor C, Kabbaj M, Akil H, Watson SJ. Delayed effects of chronic variable stress during peripubertal-juvenile period on hippocampal morphology and on cognitive and stress axis functions in rats. *Hippocampus.* 2004; 14:636–648. [PubMed: 15301440]
- Jordan CJ, Andersen SL. Sensitive periods of substance abuse: early risk for the transition to dependence. *Dev Cogn Neurosci.* 2017; 25:29–44. [PubMed: 27840157]
- Juraska JM, Willing J. Pubertal onset as a critical transition for neural development and cognition. *Brain Res.* 2017; 1654:87–94. [PubMed: 27060769]
- Karatsoreos IN, McEwen BS. Psychobiological allostasis: resistance, resilience and vulnerability. *Trend Cogn Sci.* 2011; 15:576–584.
- Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lees S, Ustun TB. Age of onset of mental disorders: a review of recent literature. *Curr Opin Psychiatr.* 2007; 20:359–364.
- Lachuer J, Delton I, Buda M, Tappaz M. The habituation of brainstem catecholaminergic groups to chronic daily restraint stress is stress specific like that of the hypothalamic-pituitary-adrenal axis. *Brain Res.* 1994; 638:196–202. [PubMed: 8199859]
- Lee FS, Heimer H, Giedd JN, Lein ES, Sestan N, Weinberger DR, Casey BJ. Adolescent mental health—opportunity and obligation. *Science.* 2014; 346:547–549. [PubMed: 25359951]
- Lui P, Padow VA, Franco D, Hall BS, Park B, Klein ZA, Romeo RD. Divergent stress-induced neuroendocrine and behavioral responses prior to puberty. *Physiol Behav.* 2012; 107:104–111. [PubMed: 22728428]
- Luna B, Garver KE, Urban TA, Lazar NA, Sweeney JA. Maturation of cognitive processes from late childhood to adulthood. *Child Dev.* 2004; 75:1357–1372. [PubMed: 15369519]
- Marceau K, Ruttle PL, Shirtcliff EA, Essex MJ, Susman EJ. Developmental and contextual considerations for adrenal and gonadal hormone functioning during adolescence: implications for adolescent mental health. *Dev Psychobiol.* 2015; 57:742–768. [PubMed: 24729154]
- McCormick CM, Green MR. From the stressed adolescent to the anxious and depressed adult: investigations in rodent models. *Neuroscience.* 2013; 249:242–257. [PubMed: 22967838]
- McCormick CM, Green MR, Simone JJ. Translational relevance of rodent models of hypothalamic-pituitary-adrenal function and stressors in adolescence. *Neurobiol Stress.* 2016; 6:31–43. [PubMed: 28229107]
- McCormick CM, Hodges TE, Simone JJ. Peer pressure: social instability stress in adolescence and social deficits in adulthood in a rodent model. *Dev Cogn Neurosci.* 2015; 11:2–11. [PubMed: 24830945]

- McCormick CM, Mathews IZ. HPA function in adolescence: role of sex hormones in its regulation and the enduring consequences of exposure to stressors. *Pharmacol Biochem Behav.* 2007; 86:220–233. [PubMed: 16901532]
- McCormick CM, Mathews IZ, Thomas C, Waters P. Investigations of HPA function and the enduring consequences of stressors in adolescence in animal models. *Brain Cogn.* 2010; 72:73–85. [PubMed: 19616355]
- Minhas S, Liu C, Galdamez J, So VM, Romeo RD. Stress-induced oxytocin release and oxytocin cell number and size in prepubertal and adult male and female rats. *Gen Comp Endocrinol.* 2016; 234:103–109. [PubMed: 26972154]
- Ogden CL, Carroll MD, Lawman HG, Fryar CD, Kruszon-Moran D, Kit BK, Flegal KM. Trends in obesity prevalence among children and adolescents in the United States, 1988–1994 through 2013–2014. *J Am Med Assoc.* 2016; 315:2292–2299.
- Ojeda, SR., Urbanski, HF. Puberty in the rat. In: Knobil, E., Neill, JD., editors. *The Physiology of Reproduction*. Raven Press; New York: 1994. p. 363–409.
- Patel, R., Romeo, RD. Pubertal- and sex-dependent changes in the hormonal concentration of the pituitary and adrenal glands. *Endocrine Society Abstract*; 2016. SUN 408
- Pattwell SS, Duhoux S, Hartley CM, Johnson DC, Jing D, Elliot MD, Ruberry EJ, Powers A, Mehta N, Yang RR, Soliman F, Glatt CE, Casey BJ, Ninan I, Lee FS. Altered fear learning across development in both mouse and human. *Proc Natl Acad Sci USA.* 2012; 109:16318–16323. [PubMed: 22988092]
- Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? *Nat Rev Neurosci.* 2008; 9:947–957. [PubMed: 19002191]
- Pecoraro N, Dallman MF, Warne JP, Ginsberg AB, Laugero KD, la Fleur SE, Houshyar H, Gomez F, Bhargava A, Akana SF. From Malthus to motive: how the HPA axis engineers the phenotype, yoking needs to wants. *Prog Neurobiol.* 2006; 79:247–340. [PubMed: 16982128]
- Peiper NC, Ridenour TA, Hochwalt B, Coyne-Beasley T. Overview on prevalence and recent trends in adolescent substance use and abuse. *Child Adol Psychiatr Clin North Am.* 2016:25.
- Pellis SM, Pellis VC. Rough-and-tumble play and the development of the social brain. *Curr Dir Psychol Sci.* 2007; 16:95–98.
- Peters A, McEwen BS, Friston K. Uncertainty and stress: why it causes disease and how it is measured by the brain. *Prog Neurobiol.* in press.
- Pham L, Baker MR, Shahanoor Z, Romeo RD. Adolescent changes in hindbrain noradrenergic A2 neurons in male rats. *Brain Res.* 2017; 1666:11–16. [PubMed: 28435085]
- Plotsky PM. Facilitation of immunoreactive corticotropin-releasing factor secretion into the hypophyseal-portal circulation after activation of catecholaminergic pathways or central norepinephrine injection. *Endocrinology.* 1987; 121:924–930. [PubMed: 3497798]
- Plotsky PM, Cunningham ET, Widmaier EP. Catecholaminergic modulation of corticotropin-releasing factor and adrenocorticotropin secretion. *Endo Rev.* 1989; 10:437–458.
- Rohner-Jeanrenaud F. Neuroendocrine regulation of nutrient partitioning. *Ann NY Acad Sci.* 1999; 892:261–271. [PubMed: 10842667]
- Romeo RD. The teenage brain: the stress response and the adolescent brain. *Curr Dir Psychol Sci.* 2013; 22:140–145. [PubMed: 25541572]
- Romeo RD. The impact of stress on the structure of the adolescent brain: implications for adolescent mental health. *Brain Res.* 2017; 1654:185–191. [PubMed: 27021951]
- Romeo RD, Ali FS, Karatsoreos IN, Bellani R, Chhua N, Vernov M, McEwen BS. Glucocorticoid receptor mRNA expression in the hippocampal formation of male rats before and after pubertal development in response to acute and repeated stress. *Neuroendocrinology.* 2008; 87:160–167. [PubMed: 17923777]
- Romeo RD, Bellani R, Karatsoreos IN, Chhua N, Vernov M, Conrad CD, McEwen BS. Stress history and pubertal development interact to shape hypothalamic pituitary adrenal axis plasticity. *Endocrinology.* 2006a; 147:1664–1674. [PubMed: 16410296]
- Romeo RD, Bellani R, McEwen BS. Stress-induced progesterone secretion and progesterone receptor immunoreactivity in the paraventricular nucleus are modulated by pubertal development in male rats. *Stress.* 2005; 8:265–271. [PubMed: 16423715]

- Romeo RD, Kaplowitz ET, Ho A, Franco D. The influence of puberty on stress reactivity and forebrain glucocorticoid receptor levels in inbred and outbred strains of male and female mice. *Psychoneuroendocrinology*. 2013; 38:592–596. [PubMed: 22917621]
- Romeo RD, Karatsoreos IN, Jasnow AM, McEwen BS. Age- and stress-induced changes in corticotropin-releasing hormone mRNA expression in the paraventricular nucleus of the hypothalamus. *Neuroendocrinology*. 2007; 85:199–206. [PubMed: 17505125]
- Romeo RD, Karatsoreos IN, McEwen BS. Pubertal maturation and time of day differentially affect behavioral and neuroendocrine responses following an acute stressor. *Horm Behav*. 2006b; 50:463–468. [PubMed: 16836997]
- Romeo RD, Lee SJ, Chhwa N, McPherson CR, McEwen BS. Testosterone cannot activate an adult-like stress response in prepubertal male rats. *Neuroendocrinology*. 2004a; 79:125–132. [PubMed: 15103225]
- Romeo RD, Lee SJ, McEwen BS. Differential stress reactivity in intact and ovariectomized prepubertal and adult female rats. *Neuroendocrinology*. 2004b; 80:387–393. [PubMed: 15741744]
- Romeo RD, Minhas S, Svirsky SE, Hall BS, Savenkova M, Karatsoreos IN. Pubertal shifts in adrenal responsiveness to stress and adrenocorticotrophic hormone in male rats. *Psychoneuroendocrinology*. 2014; 42:146–152. [PubMed: 24636511]
- Romeo RD, Patel R, Pham L, So VM. Adolescence and the ontogeny of the hormonal stress response in male and female rats and mice. *Neurosci Biobehav Rev*. 2016; 70:206–216. [PubMed: 27235079]
- Romeo RD, Richardson HN, Sisk CL. Puberty and the maturation of the male brain and sexual behavior: recasting a behavioral potential. *Neurosci Biobehav Rev*. 2002; 26:379–389.
- Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endo Rev*. 2000; 21:55–89.
- Sawchenko PE, Swanson LW. The organization of forebrain afferents to the paraventricular and supraoptic nuclei of the rat. *J Comp Neurol*. 1983; 218:121–144. [PubMed: 6886068]
- Schapiro S, Percin CJ, Kotichas FJ. Half-life of plasma corticosterone during development. *Endocrinology*. 1971; 89:284–286. [PubMed: 5089660]
- Spear LP. The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev*. 2000; 24:417–463. [PubMed: 10817843]
- Spear LP. Heightened stress responsivity and emotional reactivity during pubertal maturation: implications for psychopathology. *Dev Psychopathol*. 2009; 21:87–97. [PubMed: 19144224]
- Spinedi E, Chisari A, Pralong F, Gaillard RC. Sexual dimorphism in the mouse hypothalamic-pituitary-adrenal axis function after endotoxin and insulin stresses during development. *Neuroimmunomodulation*. 1997; 4:77–83. [PubMed: 9483198]
- Suzuki S, Oh C, Nakano K. Pituitary-dependent and -independent secretion of CS caused by bacterial endotoxin in rats. *Am J Physiol*. 1986; 250:E470–E474. [PubMed: 3008571]
- Szafarczyk A, Malaval F, Laurent A, Gibaud R, Assenmacher I. Further evidence for a central stimulatory action of catecholamines on adrenocorticotropin release in the rat. *Endocrinology*. 1987; 121:883–892. [PubMed: 3040380]
- Tielbeek JJ, Al-Itejawi Z, Zijlmans J, Polderman TJ, Buckholtz JW, Popma A. The impact of chronic stress during adolescence on the development of aggressive behavior: a systematic review on the role of the dopaminergic system in rodents. *Neurosci Biobehav Rev*. in press.
- Tottenham N, Galvan A. Stress and the adolescent brain: amygdala-prefrontal cortex and ventral striatum as developmental targets. *Neurosci Biobehav Rev*. 2016; 70:217–227. [PubMed: 27473936]
- Turner RJ, Lloyd DA. Stress burden and the lifetime incidence of psychiatric disorder in young adults. *Arch Gen Psychiatr*. 2004; 61:481–488. [PubMed: 15123493]
- Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci*. 2009; 10:397–409. [PubMed: 19469025]
- Vazquez DM. Stress and the developing limbic-hypothalamic-pituitary-adrenal axis. *Psychoneuroendocrinology*. 1998; 23:663–700. [PubMed: 9854741]

- Vazquez DM, Akil H. Pituitary-adrenal response to ether vapor in the weanling animal: characterization of the inhibitory effect of glucocorticoids on adrenocorticotropin secretion. *Pediatr Res.* 1993; 34:646–653. [PubMed: 8284104]
- Viau V. Functional cross-talk between the hypothalamic- pituitary-gonadal and -adrenal axes. *J Neuroendocrinol.* 2002; 14:506–513. [PubMed: 12047726]
- Viau V, Bingham B, Davis J, Lee P, Wong M. Gender and puberty interact on the stress-induced activation of parvocellular neurosecretory neurons and corticotropin-releasing hormone messenger ribonucleic acid expression in the rat. *Endocrinology.* 2005; 146:137–146. [PubMed: 15375029]
- Viau V, Meaney MJ. The inhibitory effect of testosterone on hypothalamic-pituitary-adrenal responses to stress is mediated by the medial preoptic area. *J Neurosci.* 1996; 16:1866–1876. [PubMed: 8774455]
- Weintraub A, Singaravelu J, Bhatnagar S. Enduring and sex-specific effects of adolescent social isolation in rats on adult stress reactivity. *Brain Res.* 2010; 1343:83–92. [PubMed: 20438720]
- Wright LD, Hebert KE, Perrot-Sinal TS. Periadolescent stress exposure exerts long-term effects on adult stress responding and expression of prefrontal dopamine receptors in male and female rats. *Psychoneuroendocrinology.* 2008; 33:130–142. [PubMed: 18065159]

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

Figure 1.

A schematic timeline of pubertal and adolescent development in rodents, such as rats in mice, including pre-adolescent (25–35 day of age), mid-adolescent (36–50 days of age), late-adolescent (51–64 days of age), and adulthood (≥65 days of age). Note that the exact age ranges that span particular stages of pubertal, adolescent, or adult development would need to take several factors into account, such as species, sex, and variable measured, as these factors could require contracting or expanding these general timeframes.

Figure 2.

Plasma ACTH (pg/ml; top panel) and corticosterone (ng/ml; bottom panel) concentrations in pre-adolescent (28 days of age) and adult (77 days of age) male rats before, during, or after a 30 min session of restraint stress (black bar under x-axis). Asterisks indicate a significant difference between the pre-adolescent and adult animals at that time point. Redrawn from (Romeo et al., 2004a).

Figure 3.

Plasma ACTH (pg/ml; top panel) and corticosterone (ng/ml; bottom panel) concentrations in male rats spanning adolescence and adulthood (30, 40, 50, 60, and 70 days of age) before, during, or after a 30 min session of restraint stress (black bar under x-axis). Asterisks in the top panel indicate a significant difference from the 60- and 70-day-old animals at that time point, while “#” indicates 30-day-old animals are significantly different from all other ages at that time point. Redrawn from (Foilb et al., 2011).

Figure 4.

Plasma corticosterone (ng/ml) concentrations in pre-adolescent (28 days of age) and adult (77 days of age) male rats before or after a single or repeated exposure to a 30 min session of restraint stress (RS; black bar under x-axis). Bars that share a letter are not significantly different from one another. Redrawn from (Romeo et al., 2006a).

Figure 5.

Number of FOS positive cells/40,000 μm^2 (top panels) and CRH and FOS double-labeled cells in the PVN (bottom panels) of pre-adolescent (28 days of age) and adult (77 days of age) male rats before or after a single (left panels) or repeated (right panels) exposure to a 30 min session of restraint stress (RS; black bar under x-axis). Asterisks indicate a significant difference between the pre-adolescent and adult animals at that time point. Redrawn from (Romeo et al., 2006a).

Figure 6.

Photomicrographs of GR positive cells in pre-adolescent (28 days of age; left panels) and adult (77 days of age; right panels) male rats in the mPFC (A and B), PVN (C and D), CA1 (E and F), and dentate gyrus (G and H) of the hippocampal formation. Abbreviations: I, layer I of mPFC; II/III, layers II and III of mPFC; 3v, third ventricle. Scale bar, 100µm. Redrawn from (Dziedzic et al., 2014).

Figure 7.

Regression analysis of plasma corticosterone (ng/ml) and ACTH in pre-adolescent (30 days of age; open circles) and adult (70 days of age; black circles) male rats 60 min after injection with ACTH. Redrawn from (Romeo et al., 2014).

Figure 8.

Plasma progesterone (ng/ml; top panel) and testosterone (ng/ml; bottom panel) concentrations in pre-adolescent (28 days of age) and adult (77 days of age) male rats before, during, or after a 30 min session of restraint stress (black bar under x-axis). Asterisks indicate a significant difference between the pre-adolescent and adult animals at that time point. Note the decrease in testosterone secretion in the pre-adolescent animals between the basal and 0 min time points. Redrawn from (Romeo et al., 2004a; Romeo et al., 2005).