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Review article

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 (HPA) 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 stressors 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, ultimately providing them with greater opportunities to mature into healthy adults.

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.

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., 2017), 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-pituitaryadrenal (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 adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn, leads to the release of glucocorticoids (i.e., cortisol in primates

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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-adolescent 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 (Fig. 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).

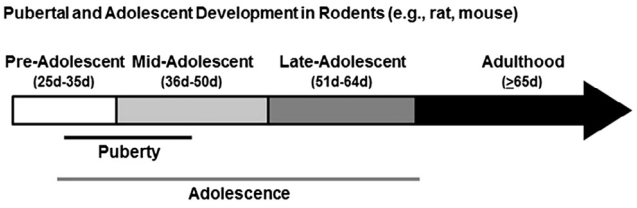

Fig. 1. A schematic timeline of pubertal and adolescent development in rodents, such as rats and mice, including pre-adolescent (25–35 day of age), mid-adolescent (36–50 days of age), late-adolescent (51–64 days of age), and adulthood (≥ 65 days of age). Note that the exact age ranges that span particular stages of pubertal, adolescent, or adult development would need to take several factors into account, such as species, sex, and the variable measured, as these factors could require contracting or expanding these general timeframes.

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; Fig. 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 and 60 days of age, while corticosterone responses shift between 30 and