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Translational relevance of rodent models of hypothalamic-pituitary-adrenal function and stressors in adolescence

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ABSTRACT

Elevations in glucocorticoids that result from environmental stressors can have programming effects on brain structure and function when the exposure occurs during sensitive periods that involve heightened neural development. In recent years, adolescence has gained increasing attention as another sensitive period of development, a period in which pubertal transitions may increase the vulnerability to stressors. There are similarities in physical and behavioural development between humans and rats, and rats have been used effectively as an animal model of adolescence and the unique plasticity of this period of ontogeny. This review focuses on benefits and challenges of rats as a model for translational research on hypothalamic-pituitary-adrenal (HPA) function and stressors in adolescence, highlighting important parallels and contrasts between adolescent rats and humans, and we review the main stress procedures that are used in investigating HPA stress responses and their consequences in adolescence in rats. We conclude that a greater focus on timing of puberty as a factor in research in adolescent rats may increase the translational relevance of the findings.

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1. Introduction

Glucocorticoid hormones (mostly cortisol in humans and corticosterone in rats), the release of which is under the control of

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the hypothalamic-pituitary-adrenal (HPA) axis, initiate mechanisms that enable the individual to adapt to the immediate demands of the environment. For example, elevations in glucocorticoids that result from the activation of the HPA axis in response to stressors have immunosuppressive and anti-inflammatory effects, influence lipid and glucose metabolism, and inhibit reproductive functions. In the CNS, through actions on neurogenesis, synaptic and dendritic remodeling, neurotransmission, and learning and memory functions, glucocorticoids shape future brain function and behaviour. Programming effects of stress exposures on the developing fetus provide a means by which glucocorticoids experienced in early life have effects across the lifespan and possibly into future generations (Bale, 2014; Meaney et al., 2007). The preclinical literature has made great inroads into mechanisms involved in the maladaptive consequences of excessive glucocorticoid exposures in early life and in adulthood that result from repeated or chronic stressors, or a severe stress exposure. So, why the interest in the adolescent period, an interest that has grown exponentially in the last 15 years?

Adolescence is of great clinical importance. It is the time in which many mental health problems such as mood disorders emerge. Further, the risk of drug abuse and addiction is greater from drug exposures in adolescence than in adulthood (e.g., Blomeyer et al., 2013). The clinical problems of many adult psychiatric patients originate in adolescent experiences (Oldehinkel and Bouma, 2011). In adolescents, as in adults, atypical HPA function and/or a history of stress exposures, are precursors to clinical depression (Guerry and Hastings, 2011). Thus, the growing interest in the adolescent period is tied to understanding risks that might be associated specifically with this time of life, a time that had been relatively neglected by researchers (Grant et al., 2003) until recently. Further, the idea that developmental plasticity (defined as a lasting phenotypic change in response to cues received in the past, Fawcett and Frankenhuis, 2015) was greatest during critical periods of prenatal and neonatal life and diminished thereafter with age is confronted with evidence that there are a series of sensitive periods across the lifespan in many species. Adolescence, specifically, has been cast as a sensitive period for the development of social functions in species as diverse as zebra finches (Ruploh et al., 2014), guinea pigs (Sachser, 1992), rats (McCormick et al., 2015), and humans (Blakemore, 2012), among others. Challenges to the view that adolescence was a specialization unique to humans (e.g., Bogin and Smith, 1996) also promoted the possibility of animal models for understanding human adolescence.

The importance of animal models for understanding mental health is well documented (Stevens and Vaccarino, 2015). This review focuses on benefits and challenges of rats as a model for translational research on hypothalamic-pituitary-adrenal function and stressors in adolescence, highlighting important parallels and contrasts between adolescent rats and humans. We also review the main stress procedures that are used in investigating HPA function and stress in adolescence in rats, and factors that should be considered for rat models of adolescent stress for translational research.

2. Pubertal development in humans and rats and the definition of adolescence

Adolescence involves a transition between childhood and adulthood, and requires a reorganization of a physiology and a behaviour repertoire that is adapted to one ontogenetic period to enable adaptations for a new ontogenetic period during which reproductive function is attained. As such, one of the important hallmarks of the adolescent period is puberty. Although there is some independence between adolescent development and the onset of puberty in that some maturational processes in the brain occur irrespective of a pubertal rise in gonadal function (Sisk and Foster, 2004), the importance of puberty to adolescence cannot be overstated. The World Health Organization defined adolescence in humans as people between the ages of 10 and 19 years, with the onset of puberty marking the transition from childhood to adolescence (http://www.who.int/maternal_child_adolescent/topics/adolescence/dev/en/).

Puberty begins at about 8–10 years of age in girls and about a year later in boys and involves a rise in kisspeptin signaling, which results in increased gonadotrophin releasing hormone release, the hypothalamic hormone of the hypothalamic-pituitary-gonadal pathway (Cortés et al., 2015). The increase in estrogenic function results in the development of breast buds in girls typically between the ages of 10 and 11 years, and menarche at about 12 years of age (Parent et al., 2003). Menarche is a relatively late manifestation of puberty that usually (but not always) is preceded by the first ovulation (Cortés et al., 2015). Further, the mean age of onset of menarche is later in underprivileged populations than in "well-off" populations (Parent et al., 2003). An increase in testicular volume is an early marker of pubertal onset in boys, and the mean age of the time of this increase is 11.5 years (Lee et al., 2010). The completion of spermatogenesis is the culmination of puberty in boys. Another feature of the pubertal process in both girls and boys is a peak in growth velocity. Growth in height ceases in girls 4–5 years after menarche at a median age of 17.3 years (Spear, 2002). The growth velocity is higher in boys and growth in height stops at a median age of 21.2 years (Spear, 2002). A 4–5 year age range in pubertal onset is considered normal variation in both sexes (Parent et al., 2003). The variation in onset of puberty in humans relative to mean life expectancy, however, is negligible compared with that in other mammals, and rats in particular (Bronson and Rissman, 1986).

One of the challenges of a preclinical model of adolescence is defining the ages that are comparable to humans. Adolescence in rats has been defined liberally as being from postnatal day (PND) 21–59 (Tirelli et al., 2003) and conservatively as being from PND 28 to 42 (Spear, 2000). There are similarities and differences in the pubertal process of rats and humans. For example, whereas the gonads are quiescent until puberty and spermatogenesis only begins at puberty in humans (Plant, 2015), in Wistar rats, spermatogenesis was found to begin at postnatal day 5 and completed at PND 43 (van Haaster and de Rooij, 1993). Comparable to the growth spurt in adolescent humans, rats have a steep increase in the length of the tibia in both males and females from about PND 25–60 and a less steep rise thereafter until reaching asymptote at about PND 175 (Horton et al., 2008). Growth rates (μm/day) in the length of the tibia are highest at about PND 45. Nevertheless, rats do not have the quiescent period in growth that is evident in humans prior to the pubertal growth spurt. Instead, in rats, skeletal growth is continuous and displays an exponential trajectory that decays at about PND 64 (Horton et al., 2008). Other markers of pubertal development than growth trajectories, however, are more commonly used in studies of adolescent rats.

Physical markers of puberty in rats that coincide with increased hypothalamic-pituitary-gonadal function are the onset of vaginal opening in females, which coincides with a surge in estradiol and the onset of ovulation (Castellano et al., 2011; Ojeda and Urbanski, 1994), and balanopreputial separation in males, which coincides with a rise in androgen concentrations and with sperm in the epididymis (reviewed in McCormick and Mathews, 2010). Regular estrous cycles typically are evident about a week after vaginal opening, and sperm production is optimal only several weeks after balanopreputial separation (Lohmiller and Sonya, 2006). Although the ages of PND 25–42 in rats has been suggested to be analogous