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Temperament moderates the influence of periadolescent social experience on behavior and adrenocortical activity in adult male rats

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ABSTRACT

Adolescence is a period of significant behavioral and physiological maturation, particularly related to stress responses. Animal studies that have tested the influence of adolescent social experiences on stress-related behavioral and physiological development have led to complex results. We used a rodent model of neophobia to test the hypothesis that the influence of adolescent social experience on adult behavior and adrenocortical function is modulated by pre-adolescent temperament. Exploratory activity was assessed in 53 male Sprague–Dawley rats to classify temperament and then they were housed in one of the three conditions during postnatal days (PND) 28–46: (1) with familiar kin, (2) with novel social partners, or (3) individually with no social partners. Effects on adult adrenocortical function were evaluated from fecal samples collected while rats were individually-housed and exposed to a 1-hour novel social challenge during PND 110–114. Adolescent-housing with novel or no social partners led to reduced adult glucocorticoid production compared to adolescent-housing with familiar littermates. Additionally, highly-exploratory pre-weanling rats that were housed with novel social partners during adolescence exhibited increased exploratory behavior and a more rapid return to basal glucocorticoid production in adulthood compared to those housed with familiar or no social partners during adolescence and compared to low-exploratory rats exposed to novel social partners. In sum, relatively short-term adolescent social experiences can cause transient changes in temperament and potentially longer-term changes in recovery of glucocorticoid production in response to adult social challenges. Furthermore, early temperament may modulate the influence of adolescent experiences on adult behavioral and adrenocortical function.

Introduction

Adolescence is a unique period for social and adrenocortical development; it is a period when non-familial social experiences become more frequent while significant neuronal and adrenocortical maturation is occurring (Douglas et al., 2004; Romeo, 2010; Spear, 2000). In particular, the acute glucocorticoid response in human and rodent adolescents requires a longer period to return to baseline levels compared to adults and prepubertal youth, and this may be an important developmental period for programming of adult adrenocortical responses (Folib et al., 2011; Romeo, 2010; Stroud et al., 2009; Walker et al., 2001). Adaptations to current and future environments are also driven by adolescent social experiences and interact with glucocorticoid hormones to shape adult behavioral profiles (Sachser et al., 2013).

The rodent adolescent period is typically defined as postnatal day (PND) 28–46, with a characteristic increase in non-familial social interactions first evident at approximately PND 28 (Spear, 2000), and maturation of hypothalamic–pituitary–adrenal (HPA) axis negative feedback mechanisms throughout (Romeo, 2010). Adolescent social experiences may shape adult behavior and HPA function via interactions between these two developmental phenomena.

Long-term effects of peripubertal experiences on behavioral and HPA axis profiles have been reported. For example, in rodents, adolescent chronic social stress (isolation, social reorganization, subordination during PND 28–70+) causes protracted corticosterone (CORT) responses and elevated basal CORT levels in adulthood and these effects can be prevented by anti-depressant (paroxetine) or corticotropin-releasing hormone 1 receptor antagonist (DMP696) administration during the stress procedure (Ros-Simó and Valverde, 2012; Schmidt et al., 2007; Sterlemann et al., 2008; Toth et al., 2011). However, models of adolescent

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stress are highly variable (e.g. social vs. physical stressor, and novel social partners vs. social isolation), and outcomes of these models are inconsistent with numerous reports of unaffected adult adrenocortical activity after peripubertal stress (Isgor et al., 2004; Lukkes et al., 2009; McCormick et al., 2004, 2008). In the current study, we tested the hypothesis that long-term influences of adolescent experiences may be temperament-specific.

Behavioral inhibition (BI) or neophobia is a relatively stable behavioral trait in humans and rodents that emerges early in development (infancy) and is characterized by fear and avoidance of novel or unfamiliar situations and objects, and heightened cortisol reactivity after exposure to psychosocial stress, novel social situations, and novel objects (Cavigelli and McClintock, 2003; Cavigelli et al., 2007; Kagan et al., 1987; Schmidt et al., 1997; Walker and Mason, 2011). In humans, this trait has been associated with increased risk of adolescent and adult mood disorders, which are often associated with altered adrenocortical regulation (e.g. Rosenbaum et al., 1993; Schwartz et al., 1999). Incidentally, some studies (human and rodent) have also shown greater glucocorticoid responses to novelty in non-inhibited (i.e. approach-oriented) individuals compared to inhibited ones (e.g. de Haan et al., 1998; Dellu et al., 1996; Stansbury and Harris, 2000), and that behavioral responses to psychological stress that are incongruent with an individual's preferred coping strategies may account for some of these seemingly contradictory findings (Stansbury and Harris, 2000; Tarullo et al., 2011). For example, in a novel peer interaction test children who exhibited behavior that was incongruent with their self-reported peer competence had larger HPA responses than children exhibiting congruent behavior, regardless of temperament (Stansbury and Harris, 2000). Furthermore, increased HPA activity was observed for highly inhibited children who were more social than those that were less social, and for uninhibited children who were less social than their uninhibited counterparts (Tarullo et al., 2011). Given increased fear-related responses to novel experiences, BI or neophobia may represent a specific trait that modulates how particular adolescent social experiences (novel social partners vs. lack of social partners) shape adult behavior and adrenocortical regulation. In the present study, we used a rodent model of neophobia to experimentally test the influence of several different adolescent social experiences (familiar kin partners, novel social partners, and no social partners) on the development of adult behavioral responses and glucocorticoid responses to novelty. We predicted that individuals that do not readily engage novelty (neophobic) will exhibit greater adrenocortical upregulation after complex, novel adolescent experiences (e.g. exposure to novel social partners) compared to after simple adolescent experiences (e.g. social isolation or familiar social partners). Additionally, we predicted that individuals that readily engage novelty (neophilic) will exhibit adrenocortical upregulation in response to simple adolescent environments such as social isolation compared to more complex social experiences like exposure to novel partners.

Previously we found that rat (Sprague–Dawley) neophobia/philia, characterized by locomotion in an unfamiliar and protected arena, was related to latency to approach novelty, and was moderately stable from pre-weaning age throughout adulthood, and was reproducible across studies (Cavigelli and McClintock, 2003; Cavigelli et al., 2007, 2009). Neophobic or inhibited males also had greater plasma CORT responses to novelty and stress compared with neophilic or non-inhibited males (Cavigelli and McClintock, 2003; Cavigelli et al., 2007; Díaz-Morán et al., 2013; Qi et al., 2010; Takahashi, 1992; Veenema et al., 2005; c.f. Dellu et al., 1996). Furthermore, neophobia is associated with decreased voluntary interactions with enriched environments and early environmental conditions can influence the development of this trait and its associated glucocorticoid profile (Tang et al., 2012). To our knowledge no one has assessed whether adolescent social experiences modify the development of this trait, and/or if this temperament dimension modifies the influence of adolescent social experiences on behavioral and glucocorticoid development into adulthood.

We tested an interactional 'temperament × adolescent social experience' hypothesis — i.e. that temperament modulates the influence of adolescent social challenges on adult behavioral and glucocorticoid response development. Specifically, we tested a 'congruent–incongruent' hypothesis that neophilic rats exposed to novel, complex social experiences would be less challenged by this 'congruent' adolescent experience than neophobic rats exposed to the same novel complexity, and/or neophilic rats exposed to no social partners (i.e. 'incongruent' with their temperament), and that temperament-adolescent 'incongruent' experiences will lead to relatively long-term upregulation of glucocorticoid production. In addition, because previous work showed that temperamental traits observed in rodents and humans can be stable throughout life, we expected that locomotion in a novel environment would be relatively stable within individuals during the peripubertal and young adult periods, but that this behavioral trait may be modulated by adolescent social experiences.

Methods

Animals

Fifty-three male Sprague–Dawley rats from 15 litters were housed in solid-bottom plastic cages (43.5 × 23.5 × 20.5 cm). Rats were maintained on a 14L:10D lighting schedule with lights on at 2000 h (central standard time, CST) and ad libitum access to food and water. Cages were cleaned twice a week by trained animal facility personnel. The colony room was maintained at 22 °C with ~50% humidity. All methods detailed below were approved by the University of Chicago Institute for Animal Care and Use Committee and adhered to the methods specified in the *Guide for the Care and Use of Laboratory Animals* (1996).

Overall design

Rats were housed with the dam and littermates from birth (i.e. PND 0) until PND 22. At PND 18, each pup was given an individually-unique ear notch, and at PND 20 pups were tested on the exploration arena to estimate neophobia. To our knowledge, there are no studies evaluating the duration or magnitude of the effects of the ear notch procedure on subsequent locomotion, however, our personal observations of pups ear-notched at this age is that they return to original behavioral profiles within hours of the procedure. Rats were weaned at PND 22 and housed in same-sex sibling trios with similar temperament distribution in each cage (one neophobic rat, one neophilic rat, and one non-responsive rat — see 'Exploration arena' section below). During PND 28–46, rats were placed in one of three experimental adolescent social conditions: (1) a control group (KIN) in which rats remained in groups of three same-sex littermates, (2) a social reorganization group (SRO) in which three unrelated same-sex novel social partners were housed together, or (3) an individual group (IND) in which rats were housed alone. In the KIN and SRO conditions, each group included one neophobic rat, one neophilic rat, and one non-responsive rat to ensure that social experiences were similar across all cages. These housing manipulations were developed to mimic social experiences that may be considered common during adolescent development in social species (e.g. moving to a new environment, and social isolation) and were considered to be relatively short-lived and benign manipulations. On PND 46 all rats were rehoused in the original same-sex littermate trios.

To determine if adult exploratory behavior and/or glucocorticoid production were altered by these adolescent experiences and/or by a congruent–incongruent interaction between temperament and adolescent social experience, rats were again tested on the exploration arena at PND 60 and 85, and from PND 110 to 114 fecal samples were collected and analyzed for fecal corticosteroid levels (see Glucocorticoid measure section below). To sample feces from individuals and to provide a