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Pubertal shifts in adrenal responsiveness to stress and adrenocorticotropic hormone in male rats

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Abstract Studies have indicated significant pubertal-related differences in hormonal stress reactivity. We report here that prepubertal (30 days) male rats display a more protracted stress-induced corticosterone response than adults (70 days), despite showing relatively similar levels of adrenocorticotropic hormone (ACTH). Additionally, we show that adrenal expression of the ACTH receptor, melanocortin 2 receptor (*Mc2r*), is higher in prepubertal compared to adult animals, and that expression of melanocortin receptor accessory protein (*Mrap*), a molecule that chaperones MC2R to the cell surface, is greater in prepubertal males following stress. Given that these data suggest a pubertal shift in adrenal sensitivity to ACTH, we directly tested this possibility by injecting prepubertal and adult males with 6.25 or 9.375 μg/kg of exogenous rat ACTH and measured their hormone levels 30 and 60 min post-injection. As these doses resulted in different circulating levels of ACTH at these two ages, we performed regression analyses to assess the relationship between circulating ACTH and corticosterone concentrations. We found no difference between the ages in the correlation between ACTH and corticosterone levels at the 30 min time point. However, 60 min following the ACTH injection, we found prepubertal rats had significantly higher corticosterone concentrations at lower levels of ACTH compared to adults. These data suggest that prolonged exposure to ACTH leads to greater corticosterone responsiveness prior to puberty, and indicate that changes in adrenal sensitivity to ACTH may, in part, contribute to the protracted hormonal stress response in prepubertal rats.
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1. Introduction

Puberty is marked by many changes in neuroendocrine processes, resulting in significant and extensive influences on an organism's physiological and neurobehavioral function (Grumbach, 2002; Sisk and Foster, 2004; Romeo, 2005). One such pubertal-related change is the substantial shift in stress reactivity exhibited by the hypothalamic–pituitary–adrenal (HPA) axis, with peripubertal animals showing an extended hormonal stress response compared to adults (McCormick and Mathews, 2007; Romeo, 2010a,b). For example, following a variety of acute stressors, such as intermittent foot shock, ether inhalation, or restraint, prepubertal male and female rats (i.e., approximately 30 days of age) display adrenal corticosterone responses, both total and free, that last significantly longer (~40 min) than those observed in adults (i.e., greater than 65 days of age; Goldman et al., 1973; Vazquez and Akil, 1993; Romeo et al., 2004a,b,2006a,b; Foilb et al., 2011; Lui et al., 2012). Interestingly, puberty in both human and non-human animal models is also associated with increases in many stress-related physiological and psychological dysfunctions, including depression, anxiety, and drug use and abuse (Andersen, 2003; Costello et al., 2003; Dahl, 2004; Patton and Viner, 2007). Therefore, examining the basic mechanisms that mediate changes in stress reactivity during puberty may contribute to our understanding of the stress-related vulnerabilities often observed during this crucial developmental stage.

The factors that mediate the pubertal change in corticosterone reactivity to stress are presently unclear. As adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary is one of the major signals regulating the release of adrenal corticosterone under stressful conditions (Herman et al., 2003; Bornstein et al., 2008), the slightly higher stress-induced plasma ACTH levels found in prepubertal compared to adult animals may contribute to the age-related difference in corticosterone (Vazquez and Akil, 1993; Romeo et al., 2004a,b). It would appear, however, that a difference in ACTH levels is not the only mediator of the prolonged corticosterone response in prepubertal rats. First, the magnitude of the age-dependent change in stress-evoked ACTH is much smaller than the changes in corticosterone (Vazquez and Akil, 1993; Romeo et al., 2004a,b). Second, and perhaps more importantly, a recent study reported that post-stress ACTH levels are similar across peripubertal animals between 30 and 50 days, while corticosterone levels were only significantly higher in 30 day old animals (Foilb et al., 2011). As the rate of corticosterone metabolism is similar in peripubertal and adult rats (Schapiro et al., 1971), these data would suggest that pubertal shifts in adrenal responsiveness to ACTH contribute to the prolonged hormonal response observed prior to puberty.

The purpose of the present set of experiments was to test the hypothesis that the greater stress-induced corticosterone response in prepubertal animals is due to increased sensitivity of the prepubertal adrenal glands to ACTH. More specifically, we predict that exogenously administered ACTH will lead to a significantly greater corticosterone response in prepubertal compared to adult rats. We also examined stress-induced changes in the expression of melanocortin 2 receptor (*Mc2r*) and melanocortin 2 receptor accessory protein (*Mrap*) mRNA in the prepubertal and adult adrenal gland. MC2R is the receptor for ACTH that when stimulated leads to the production and release of corticosterone from the adrenal gland, while MRAP is an accessory protein to MC2R that helps chaperone the receptor to the membrane surface (Hinkle and Sebag, 2009; Webb and Clark, 2010; Cooray and Clark, 2011). Therefore, based on our prediction of greater ACTH sensitivity prior to puberty, we also hypothesized that prepubertal animals exposed to stress would demonstrate greater expression levels of adrenal *Mc2r* and/or *Mrap* compared to adults.

2. Materials and methods

2.1. Animals and housing

Male Sprague-Dawley rats were obtained from Charles River (Wilmington, MA) at 21 days of age, housed 2 per cage in clear polycarbonate cages (45 × 25 × 20 cm) with wood chip bedding, and were maintained on a 12 h light–dark schedule (lights on at 0900 h). All animals had free access to food and water and the animal room was maintained at 21 ± 2 °C. All procedures were carried out in accordance with the guidelines established by the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee (IACUC) of Columbia University.

2.2. Experimental design

Two experiments were conducted. Experiment 1 measured the stress-induced ACTH and corticosterone response, as well as changes in adrenal *Mc2r* and *Mrap* expression, in prepubertal (30 days of age) and adult (70 days of age) male rats before, during, and after a 30 min session of restraint stress. Experiment 2 examined the relationship between exogenously administered ACTH and corticosterone secretion in prepubertal and adult male rats, as well as any changes in plasma testosterone levels.

In Experiment 1, prepubertal and adult rats were weighed and rapidly decapitated by a guillotine either before or after a 30 min session of restraint stress. Two time points after the 30 min restraint stress session were examined: immediately after termination of the stressor or 30 min after the stress session (n = 6 per age and time point). These ages and time points were chosen based on previously published studies investigating pubertal-related changes in hormonal stress reactivity (Goldman et al., 1973; Vazquez and Akil, 1993; Romeo et al., 2004a). The restraint stress was administered by placing animals in the prone position in wire mesh restrainers, sized so that animals at these different ages were equally restrained. Trunk blood samples were collected in EDTA-coated tubes (Vacutainer K3; Fisher Scientific, Pittsburgh, PA), spun down for 10 min at 2500 rpm in a refrigerated centrifuge, and plasma was removed and stored at −20 °C until radioimmunoassays were performed (see below). Adrenal glands were cleaned of fat, weighed, snap frozen on powdered dry ice, and stored at −80 °C until they were prepared for determination of *Mc2r* or *Mrap* mRNA levels by RT-qPCR (see below). In regards to *Mrap*, we did not measure the recently characterized *Mrap2*, as studies in

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