Social Instability Stress in Adolescent Male Rats Alters Hippocampal Neurogenesis and Produces Deficits in Spatial Location Memory in Adulthood

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ABSTRACT: The ongoing development of the hippocampus in adolescence may be vulnerable to stressors. The effects of social instability stress (SS) in adolescence (daily 1 h isolation and change of cage partner postnatal days 30–45) on cell proliferation in the dentate gyrus (DG) in adolescence (on days 33 and 46, experiment 1) and in adulthood (experiment 2) was examined in Long Evans male rats and compared to nonstressed controls (CTL). Additionally, in experiment 2, a separate group of SS and CTL rats was tested on either a spatial (hippocampal-dependent) or nonspatial (nonhippocampal dependent) version of an object memory test and also were used to investigate hippocampal expression of markers of synaptic plasticity. No memory impairment was evident until the SS rats were adults, and the impairment was only on the spatial test. SS rats initially (postnatal day 33) had increased cell proliferation based on counts of Ki67 immunoreactive (ir) cells and greater survival of immature neurons based on counts of doublecortin ir cells on day 46 and in adulthood, irrespective of behavioral testing. Counts of microglia in the DG did not differ by stress group, but behavioral testing was associated with reduced microglia counts compared to nontested rats. As adults, SS and CTL rats did not differ in hippocampal expression of synaptophysin, but compared to CTL rats, SS rats had higher expression of basal calcium/calmodulin-dependent kinase II (CamKII), and lower expression of the phosphorylated CamKII subunit threonine 286, signaling molecules related to synaptic plasticity. The results are contrasted with those from previous reports of chronic stress in adult rats, and we conclude that adolescent stress alters the ongoing development of the hippocampus leading to impaired spatial memory in adulthood, highlighting the heightened vulnerability to stressors in adolescence. © 2011 Wiley-Liss, Inc.

KEY WORDS: doublecortin; Ki67; microglia; calcium/calmodulin-dependent kinase II; synaptophysin

INTRODUCTION

The hippocampus retains structural plasticity, such as remodeling of dendrites and synapses in the pyramidal layer and neurogenesis in the dentate gyrus (DG), throughout life [reviewed in McEwen (2010)]. The role of glucocorticoid hormones (commonly referred to as stress hormones) in mediating the influence of the environment on the functional and structural plasticity of the hippocampus has been investigated extensively. Nonetheless, investigations of the role of stressors and stress hormones in shaping hippocampal structure and function during adolescence in animal models have been relatively few until recent years [reviewed in McCormick et al. (2010a)]. There is, however, much reason to suspect that the effects of stressors and stress hormones would have different consequences in adolescence (generally considered between postnatal days 28 and 59 in rats) than in adulthood (more than postnatal day 59). There are notable differences between adolescents and adults in the hypothalamic-pituitary-adrenal (hypothalamo-pituitary-adrenal (HPA) axis, the activation of which culminates in the release of glucocorticoid hormones. For example, corticosterone release in response to stressors is prolonged in adolescence compared to in adulthood, and HPA function is insensitive in early adolescence to regulation by sex hormones, which is evident in adulthood [reviewed in Romeo (2010)].

In addition, the hippocampus changes significantly during adolescence. For example, neurogenesis and the density of dendritic spines are higher in early adolescence and begin to decline to adult levels soon after puberty (He and Crews, 2007; Yildirim et al., 2008). There is evidence of differences in signaling cascades in adolescents compared to adults, with changes in the composition of signaling proteins in the hippocampus occurring in adolescence (Weitzdorfer et al., 2008). Furthermore, there are differences between adolescents and adults in performance of hippocampal-dependent behavioral tasks [reviewed in McCormick and Mathews (2010)]. Thus, the ongoing development of the hippocampus may render it more malleable in adolescence than in adulthood.

In one of the few investigations of the enduring consequences of stressors in adolescence that has included an adult-stressed comparison group, we

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