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Sex differences and the modulating effects of gonadal hormones on basal and the stressor-decreased newly proliferative cells and neuroblasts in dentate gyrus

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Summary This study was undertaken to assess sex differences and the modulating effects of gonad intactness and the estrous phase on basal and the stressor-decreased cell proliferation and early differentiation in Balb/C mouse dentate gyrus (DG). Besides, we compared the stress-reversing effects exerted by the presence of male and female Balb/C mouse odors in stressed male and female mouse DG in this regard. Female mice had lower baselines in the number of newly proliferated cells and neuroblasts than male mice. Although the stressor induced decreases in the number of newly proliferative cells and neuroblasts in both male and female DG, an obvious decrease in neuronal lineage commitment was observed in female DG. Moreover, ovariectomy induced decreases in baselines in the number of proliferative cells and neuroblasts but did not affect the stressor-induced decrease in neuronal lineage commitment in female DG. Interestingly, pro-estrous mice exhibited the stressor-decreased neuronal lineage commitment, while estrous and diestrous mice did not display such a decrease. Furthermore, orchidectomy did not affect basal or the stressor-decreased newly proliferative cells or neuroblasts in male DG. Finally, male odors were less effective than female odors in abolishing the stressor-decreased neuronal lineage commitment in female mice, while male and female odors were comparable in reversing

Abbreviations: DG, dentate gyrus; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor.

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the stressor-decreased newly proliferated cells and neuroblasts in male mice. The protective effects of mouse odors' company in the stressed male mouse DG were associated with local BDNF and NGF replenishment. Taken together, sexual differences in baselines in the number of newly proliferative cells, neuroblasts, and the sensitivity to stress-altered neuronal lineage commitment in the DG could be, in part, due to gonadal hormone differences between the two sexes. Mouse odors may reverse stressor-decreased newly proliferative cells and neuroblasts in male, but not in female, mouse DG by restoring BDNF and NGF levels.

1. Introduction

Women are more likely than men to suffer from stress-related psychiatric disorders (Bangasser and Valentino, 2012). Likewise, many studies indicate that adult female and male mice display a variety of differences in stress vulnerability and sensitivity (Adamec et al., 2006; Buron et al., 2007). Stress and stress-induced corticosterone secretion associate negatively with cell proliferation and neurogenesis in the dentate gyrus (DG) of many experimental animals (Gould et al., 1991; Cameron and Gould, 1994; Tanapat et al., 2001; Mattson et al., 2004; Mirescu and Gould, 2006; Pawluski et al., 2009). Lately, we report that a tandem stressor regimen can acutely reduce newly cell proliferation and early neuronal differentiation in male Balb/C mouse DG (Cherng et al., 2010). Whether this stressor regimen can cause similar decreases in female mouse DG remains elusive. Several lines of evidence support the notion that stressors may affect DG cell proliferation and neurogenesis in a sex-dependent manner. For example, an acute stressor is found to decrease cell proliferation and neurogenesis in the DG in male, but not in female, rats (Falconer and Galea, 2003). Moreover, a chronic stressor decreases neurogenesis in male but increases neurogenesis in female rat DG (Westenbroek et al., 2004). Furthermore, social isolation stressor has been proven to reduce neurogenesis in the DG of male rats (Spritzer et al., 2011) and female voles (Lieberwirth et al., 2012). Forced swimming stressor decreases the survival percentage of 1-wk old neurons in female mouse DG (Llorens-Martín and Trejo, 2011). Although various types of stressors may sex-dependently affect DG cell proliferation and neurogenesis in many rodent models, sex differences in the stress-altered new cell proliferation and early neuronal differentiation remain mostly unknown for mice. In fact, sex differences in basal cell proliferation in the DG have been reported in mouse and rat models (Galea et al., 2006). For example, sex differences in basal cell proliferation in many brain regions are observed in C57BL/6 and Balb/C mice (Tatar et al., 2013). Moreover, estradiol can enhance cell proliferation in the DG of adult female rats, while testosterone does not seem to affect cell proliferation in adult male rat DG (Galea et al., 2006). Nonetheless, the modulating effects of intact gonads and the estrous phase on basal cell proliferation and neuronal differentiation in female mouse DG are scarcely explored. Sex differences in basal cell proliferation and early differentiation in the DG could be due to their differences in gonad steroids, secretory profile of gonad steroids, and the stress-stimulated corticosterone secretion (Pawluski et al., 2009). In this study, our first goal was to examine the sex differences and the modulating effects of intact gonads and estrous phase on basal and the stressor-decreased new cell proliferation, early neuronal differentiation and neuronal lineage commitment in the DG of adult female and male Balb/C mice.

Social grouping and exposure to sex-dependent odors and/or pheromones have been known to modulate the stress-decreased cell proliferation or neurogenesis. For example, a chronic stress can decrease cell proliferation in individually housed male and not in socially housed male rats, while such a chronic stress does not alter cell proliferation in female rats (Westenbroek et al., 2004). Exposure to novel male sheep odors can rapidly enhance cell proliferation in the hippocampus of female sheep (Hawken et al., 2009). Exposure to male mouse pheromones can increase the rate of neurogenesis in female mice (Mak et al., 2007). We previously demonstrate that the presence of male companions throughout a stressor regimen effectively reverses the stressor-induced decreases in the number of newly proliferated cells and proliferative neuroblasts in male mouse DG (Cherng et al., 2010). Since the main olfactory epithelium is necessary for this companion-exerted protective effect (Cherng et al., 2012), the presence of wooden blocks impregnated with male mouse odors can also reverse such stressor-induced decreases in male mouse DG (Tzeng et al., 2013). Whether the presence of female mouse odors can exert this protective effect in male mouse DG and how the odors of two sexes can modulate newly cell proliferation and early neuronal differentiation in female mouse DG remain unexplored. Thus, the second goal of this study was to assess the magnitude of the protective effects of unfamiliar female and male mouse odors against the stressor-induced decreases in the number of newly proliferated cells, early proliferative neuroblasts and neuronal lineage commitment in the DG of adult female and male mice.

2. Materials and methods

2.1. Animals

Male and female Balb/C mice were bred at National Cheng Kung University College of Medicine (NCKUCM) Laboratory Animal Center. After weaning, Balb/C mice were group housed by sex in plastic cages (six per cage) in a temperature- and humidity-controlled colony room on a 12-h light/dark cycle with lights on at 0700 h at the Center. Three wooden blocks were always placed in each cage in an attempt to reduce the likely block-produced novelty in later experiments. In this study, mice had access to food (Purina Mouse Chow, Richmond, IN, USA) and tap water ad libitum. All experiments started when mice reached 9—10 weeks of age. This study was performed in accordance with the National Institutes of Health Guide for the Care and Use of