Brain Research 1683 (2018) 78–85

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/bres

Research report

Housing environment influences stress-related hippocampal substrates and depression-like behavior

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ARTICLE INFO

Article history:
Received 22 August 2017
Received in revised form 15 January 2018
Accepted 17 January 2018

Keywords:
CA3
Enriched environment
Forced swimming
Glucocorticoids
Hippocampus
Neurogenesis

ABSTRACT

Rats are widely used animal models for biological psychiatry and neuroscience. Laboratory rats are typically housed in impoverished sensory environments. The lack of species-typical sensory environment might radically change the response of individual animals to stressful and/or threatening episodes. In this report, we demonstrate that behavioral and neural sequelae of chronic stress were modified by sensory environment of adult male rats. This includes effects of stress on the density of spines on CA3 hippocampal neurons, hippocampal neurogenesis and abundance of glucocorticoid or mineralocorticoid receptors. Enrichment also reduced depression-like behavior in a forced swim task. Stress and sensory enrichment evoked opposing effects on all the above endpoints. The sensory enrichment used in this report is of a relatively short duration provided during adulthood. This period excludes critical windows of greater plasticity during pre- and peripubertal stages. Our results suggest that standard housing practices for laboratory rats remain austere concerning sensory requirements of this species. Thus, even a moderate sensory enrichment is capable of reducing high stress-sensitivity and depressive-like behavior in standard laboratory rats.

1. Introduction

Laboratory rats are commonly used in behavioral neuroscience research. These animals are often housed in "standard" laboratory cages characterized by *ad libitum* nutrition, extensive monitoring of physical health, and the impoverished sensory environment. This housing is atypical in comparison to environment experienced by feral rats, resulting in robust behavioral consequences (Berdoy, 2002; Boice, 1977; Boice, 1981; Hughes and Boice, 1973).

Exposure to uncontrollable chronic stress enhances depression-like behavior in rats, manifested as greater anhedonia and depressive-like behavior (Wood et al., 2008). Such changes in behavior are thought to result from allostatic load produced by repeated stress response (McEwen, 2001). At the neural level, this allostatic load manifests itself as reduced synaptic connectivity (Chen et al., 2008; Chen et al., 2010c; Watanabe et al., 1992) and reduced neurogenesis (Mahar et al., 2014; Mineur et al., 2007; Pham et al., 2003) in hippocampal formation. On the other hand, provision of sensory enrichment enhances hippocampal neurogenesis (Beauquis et al., 2010; Jha et al., 2011; Olson et al., 2006; Paez-Martinez et al., 2013; Segovia et al., 2006; Tanti et al., 2013; Veena et al., 2009) and synaptic connectivity (Beauquis et al., 2010; Bindu et al., 2007; Faherty et al., 2003; Hutchinson et al., 2012; Lauterborn et al., 2015; Rojas et al., 2013), in parallel to decreasing depression-like behavior (Cui et al., 2006; Gomeni and Merlo-Pich, 2012; Grippo et al., 2014; Veena et al., 2009; Zhang et al., 2011). This would suggest that sensory enrichment and chronic stress impinge on the same biological machinery albeit in different directions. In other words, stress and enriched environment interactively determines allostatic load to bring about change in behavior and neuroanatomy. This assertion has potent implications for laboratory animal management (Mo et al., 2016; Toth, 2015).

In this report, we experimentally tested this hypothesis by estimating statistical interaction between chronic immobilization stress and a short concurrent sensory enrichment for endpoints related to depression like behavior and neuronal remodeling in the hippocampal formation. We further investigated associated changes in the levels of glucocorticoid and mineralocorticoid receptors in hippocampal formation.

2. Results

Adult male rats were exposed to stress and/or sensory enrichment. Exposure to stress reduced body weight gain of animals

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https://doi.org/10.1016/j.brainres.2018.01.021
0006-8993/

during the experimental period as evidenced by the main effect of stress in a two-way ANOVA (body weight gain normalized to weight at the start of the experiment, %; $F_{1,26} = 31.3$, $p < 0.001$). Effect of sensory enrichment ($F_{1,26} = 0.04$, $p = 0.840$) or the interaction between stress and enrichment ($F_{1,26} = 0.02$, $p = 0.890$) did not reach statistical significance. Orthogonal planned comparisons revealed significant stress-induced reduction in body weight gain in absence or presence of enrichment ($t_{26} > 3.98$, $p < 0.002$; mean difference non-stressed minus stressed >11%).

2.1. Depressive-like behavior in Porsolt forced swim task

Animals were tested for depressive-like behavior using Porsolt forced swim paradigm. Immobility in trial two was used as a proxy for depressive-like behavior (N = 8 animals in each group; data from 2 animals in stressed enriched group was unavailable due to video loss). Two-way ANOVA revealed a significant main effect of sensory enrichment on immobility ($F_{1,26} = 8.6$, $p = 0.007$; enri ched < non-enriched). Enrichment accounted for 24.1% of total variance in the design. Main effect of stress did not reach statistical significance ($F_{1,26} = 0.3$, $p = 0.598$). Similarly, interaction between stress and enrichment was not significant ($F_{1,26} = 0.8$, $p = 0.370$). Orthogonal planned comparisons were conducted to estimate effects of chronic stress in either enriched or non-enriched condition. Stress did not cause significant change in immobility in presence or absence of enrichment (Fig. 1A; $t_{26} < 1.1$, $p > 0.5$).

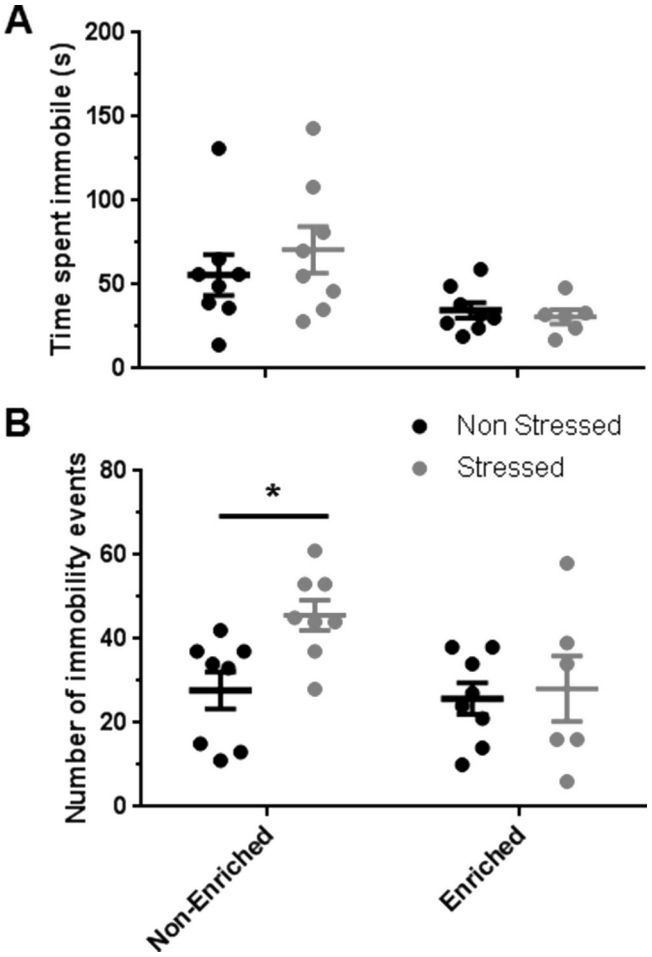

Fig. 1. Environmental enrichment reduced time spent immobile (A) and number of immobility events (B) in Porsolt forced swim paradigm. The panels depicts mean and SEM along with raw values obtained for each subject. N = 6 for 'enriched + stressed' group and 8 for all other groups. *, $p \leq 0.05$ for comparison between stressed group and the corresponding control.

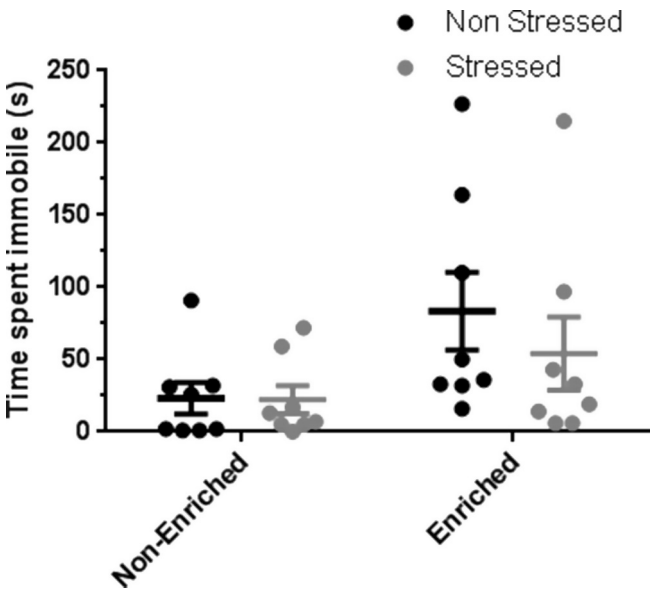

Fig. 2. Environmental enrichment increased immobility in non-threatening baseline environment. Mean, and SEM along with raw values obtained for each subject is depicted. N = 8 for all groups.

Total number of immobility events was also analyzed (ANOVA: $F_{1,26} = 4.1$, $p = 0.053$ for enrichment; $F_{1,26} = 4.4$, $p = 0.045$ for stress; $F_{1,26} = 2.6$, $p = 0.120$ for the interaction). Stress accounted for 11.7% of the total variance in the design. Planned comparisons revealed that stress increased the total number of immobility events in absence of enrichment (Fig. 1B; $t_{26} = 2.73$, $p = 0.02$); but not in presence of enrichment ($t_{26} = 0.34$, $p = 0.93$). Latency to the first immobility event did not exhibit statistically significant inter-group differences during ANOVA ($p > 0.09$) or planned comparisons ($p > 0.28$). Similarly, time spent attempting to climb the vertical walls did not exhibit statistically significant differences in ANOVA ($p > 0.08$) or planned comparisons ($p > 0.8$).

Thus, enrichment had main effect of reduced immobility ($p = 0.007$) and reduced number of immobile episodes ($p = 0.053$) in the Porsolt forced swim task. Enrichment induced reduction in immobility was specific to depression-like context of the task, and not because of a generalized motor deficit. Sensory enrichment increased baseline immobility when tested in a non-threatening environment (Fig. 2; main effect of enrichment: $F_{1,28} = 5.4$, $p = 0.028$; enriched > non-enriched). The main effect of stress and interaction of stress with enrichment were not statistically significant ($p > 0.45$). Moreover enrichment did not reduce immobility in a novel rectangular arena. Non-stressed animals exposed to enrichment made lesser sorties during the five-minute trial in the arena compared to non-stressed non-enriched animals ($t_{14} = 2.15$, $p = 0.050$; mean difference non-stressed minus stressed = −4.75 ± 2.21). Time spent immobile in the open arena was not statistically different between the groups ($t_{14} = 0.65$, $p = 0.528$; mean difference non-stressed minus stressed = −11.33 ± 17.5 s). Similarly, inter-group differences in total distance travelled during the five-minute trial was not statistically significant ($t_{14} = 1.68$, $p = 0.115$).

2.2. The density of spines on CA3 hippocampal neurons

Spine density across 60 μm of CA3 primary dendrites was quantified. Two-way ANOVA revealed a significant main effect of sensory enrichment ($F_{1,176} = 8.2$, $p = 0.005$, enriched > non-enriched). Enrichment accounted for 3.4% of the total variance in the design.