BRAIN RESEARCH 1362 (2010) 68–77

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BRAIN RESEARCH

Research Report

Physical activity, but not environmental complexity, facilitates HPA axis response habituation to repeated audiogenic stress despite neurotrophin mRNA regulation in both conditions

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ARTICLE INFO

Article history:
Accepted 10 September 2010
Available online 17 September 2010

Keywords:
Voluntary physical activity
HPA axis
Stress habituation
BDNF
In situ hybridization

ABSTRACT

Stress exacerbates several physical and psychological disorders. Voluntary exercise can reduce susceptibility to many of these stress-associated disorders. In rodents, voluntary exercise can reduce hypothalamic-pituitary-adrenocortical (HPA) axis activity in response to various stressors as well as upregulate several brain neurotrophins. An important issue regarding voluntary exercise is whether its effect on the reduction of HPA axis activation in response to stress is due to the physical activity itself or simply the enhanced environmental complexity provided by the running wheels. The present study compared the effects of physical activity and environmental complexity (that did not increase physical activity) on HPA axis habituation to repeated stress and modulation of brain neurotrophin mRNA expression. For six weeks, male rats were given free access to running wheels (exercise group), given 4 objects that were repeatedly exchanged (increased environmental complexity group), or housed in standard cages. On week 7, animals were exposed to 11 consecutive daily 30-min sessions of 98-dBA noise. Plasma corticosterone and adrenocorticotropic hormone were measured from blood collected directly after noise exposures. Tissue, including brains, thymi, and adrenal glands was collected on Day 11. Although rats in both the exercise and enhanced environmental complexity groups expressed higher levels of BDNF and NGF mRNA in several brain regions, only exercise animals showed quicker glucocorticoid habituation to repeated audiogenic stress. These results suggest that voluntary exercise, independent from other environmental manipulations, accounts for the reduction in susceptibility to stress.

1. Introduction

It is well established that stress precipitates or exacerbates several physical and psychological disorders (Brown and Harris, 1987; Pasternac and Talajic, 1991; Hammen et al., 1992; Stratakis and Chrousos, 1995; Sapolsky, 1996; Arborelius et al., 1999, 2004; Vanitallie, 2002). Among other effects, stress activates the hypothalamic-pituitary-adrenocortical (HPA) axis, which leads to the release of glucocorticoids into the general vasculature. Repeated exposure to the same stressor often diminishes HPA axis activation to that stressor, a phenomenon termed stress habituation (Marti and Armario, 1998; Grissom and Bhatnagar,

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doi:10.1016/j.brainres.2010.09.038

2009). Although glucocorticoids regulate many vital physiologic functions under normal and acute stress conditions, it is their sustained release by repeated stress that is strongly associated with disorders (Chrousos and Gold, 1992; Tsigos and Chrousos, 1994; McEwen, 2000; Charmandari et al., 2005; Jokinen and Nordstrom, 2008). Thus, stress habituation is likely an important mechanism to keep physiological and psychological functions optimal in the face of repeated stress.

Voluntary physical activity has been reported to reduce susceptibility to many stress-associated disorders (Manson et al., 1992; Chodzko-Zajko and Moore, 1994; Wannamethee et al., 1998; Fox, 1999; Dunn et al., 2001; Oguma and Shinoda-Tagawa, 2004; Kruk and Aboul-Enein, 2006). Importantly, voluntary exercise regimens moderate several stress-related responses in rodents (Greenwood et al., 2007; Greenwood and Fleshner, 2008; Day et al., 2008; Sasse et al., 2008), including HPA axis activation under some acute and repeated stress conditions (Dishman et al., 1998; Droste et al., 2007; Sasse et al., 2008; Campeau et al., 2010). Various exercise regimens have also been associated with up-regulation of neurotrophins in several brain regions, particularly in the hippocampal formation (Oliff et al., 1998; Russo-Neustadt et al., 2001; Adlard and Cotman, 2004). This is in contrast to the effects of stress, which regularly reduce neurotrophin expression (Foreman et al., 1993; Smith et al., 1995; Ueyama et al., 1997; Cirulli and Alleva, 2009; Campeau et al., 2010).

An important issue with regard to the finding that voluntary physical activity can reduce acute HPA axis activation to some stressors (Droste et al., 2007; Campeau et al., 2010), and enhance the rate or final extent of habituation to repeated stress (Sasse et al., 2008), is the exact contribution of the physical activity component to these observed effects. In these studies, isolated rats kept in an otherwise empty plastic cage were compared with rats similarly housed, but with a freely accessible running wheel. One possibility is that the impoverished condition of the isolated control rats (Rosenzweig and Bennett, 1977) is improved by the addition of the running wheel, independent of the increase in physical activity exhibited by animals housed under this condition. The consistent lack of correlation between the amount of physical activity engaged in by individual animals and their observed HPA axis responses to acute or repeated stress may support this possibility (Sasse et al., 2008; Campeau et al., 2010). The present study therefore sought to determine if simply adding complexity to isolated rats' cages, without noticeably increasing their physical activity, would also reduce acute or repeated HPA axis responses to audiogenic stress, compared to isolated rats with or without freely accessible running wheels. In addition, the effects of these manipulations on the expression of neurotrophins and their receptor mRNAs were compared following repeated stress, to obtain an independent index of the effectiveness of these different manipulations in isolated rats.

2. Results

2.1. Running data

The average daily distances (in km) run by exercise (X) animals were calculated for each week of the experiment, as shown in Fig. 1. The average daily running distances for each week are consistent with our previous observations (Sasse et al., 2008), and those of other studies employing Sprague–Dawley rats (Noble et al., 1999; Moraska and Fleshner, 2001). Running distance was not significantly correlated with gland weight, plasma glucocorticoid levels, or BDNF or NGF mRNA expression in any region.

2.2. Body weight

Animals were weighed on Days 1, 5, 12, 19, 26, 33, 40, 47, and 53. There was a significant Day × treatment interaction over the course of the study ($F_{16, 360}=9.528$, $p=0.0001$), indicating a differential weight regulation across the different treatments over time. This interaction is explained by a lack of difference between groups on Day 1 ($F_{2, 45}=0.0666$, $p=0.9357$), but reliable and increasing body weight differences thereafter ($p<0.05$). Daily post-hoc analyses found that the exercised animals gained significantly less weight compared to both the home cage control (HC) and increased environmental complexity (IC) animals (which never differed significantly from each other) beginning on Day 5 of the experiment (Tukey's HSD $ps=0.0001$), as shown in Fig. 2.

2.3. Adrenal/thymus weights

The adrenal (left and right glands together) and thymus glands were weighed following sacrifice. Gland weights were analyzed in two ways. First, a corrected weight was calculated by dividing gland weight in milligrams by individual body weight in grams. Analyses on uncorrected gland weights were also performed. There were significant differences between groups for corrected thymi and adrenals ($F_{2, 45}=3.978$, $p=0.026$, and $F_{2, 45}=5.846$, $p=0.006$, respectively). Post-hoc analyses found that the exercised animals had smaller corrected thymus weights than controls (Tukey's HSD $p=0.019$). Corrected adrenal gland weights were higher in exercised animals compared to HC and IC animals (Tukey's HSD $ps<0.05$). One way ANOVA on uncorrected values revealed significant differences between groups for thymi only ($F_{2, 45}=8.861$, $p=0.001$). Post-hoc analyses found that the exercised animals had smaller uncorrected thymi weights than control and complex cage animals (Tukey's HSD $ps<0.05$), as shown in Table 1.

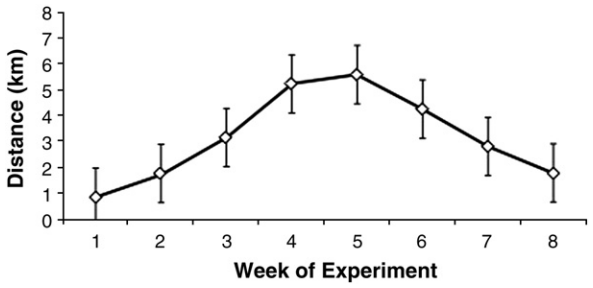

Fig. 1 – Average daily running distance (km) of exercised animals for weeks 1–8 of experiment. Repeated stress exposures took place over weeks 7 and 8.