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Research report

Cognitive and locomotor/exploratory behavior after chronic exercise in the olfactory bulbectomy animal model of depression

Jacqueline Van Hoomissen[a,*], Julie Kunrath[a], Renee Dentlinger[a], Andrew Lafrenz[a], Mark Krause[b,1], Afaf Azar[b]

[a] Department of Biology, University of Portland, 5000 North Willamette Boulevard, Portland, OR 97203-5798, USA
[b] Department of Social and Behavioral Science, University of Portland, 5000 North Willamette Boulevard, Portland, OR 97203-5798, USA

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ABSTRACT

Despite the evidence that exercise improves cognitive behavior in animal models, little is known about these beneficial effects in animal models of pathology. We examined the effects of activity wheel (AW) running on contextual fear conditioning (CFC) and locomotor/exploratory behavior in the olfactory bulbectomy (OBX) model of depression, which is characterized by hyperactivity and changes in cognitive function. Twenty-four hours after the conditioning session of the CFC protocol, the animals were tested for the conditioned response in a conditioned and a novel context to test for the effects of both AW and OBX on CFC, but also the context specificity of the effect. OBX reduced overall AW running behavior throughout the experiment, but increased locomotor/exploratory behavior during CFC, thus demonstrating a context-dependent effect. OBX animals, however, displayed normal CFC behavior that was context-specific, indicating that aversively conditioned memory is preserved in this model. AW running increased freezing behavior during the testing session of the CFC protocol in the control animals but only in the conditioned context, supporting the hypothesis that AW running improves cognitive function in a context-specific manner that does not generalize to an animal model of pathology. Blood corticosterone levels were increased in all animals at the conclusion of the testing sessions, but levels were higher in AW compared to sedentary groups indicating an effect of exercise on neuroendocrine function. Given the differential results of AW running on behavior and neuroendocrine function after OBX, further exploration of the beneficial effects of exercise in animal models of neuropathology is warranted.

1. Introduction

Chronic physical activity is an effective treatment for major depressive disorder, with a therapeutic effect similar in magnitude to more commonly used treatments, such as pharmacotherapy [1–5]. Biologically plausible neural mechanisms that explain the beneficial effect of exercise include, but are not limited to, the monoamine systems, neurotrophic factors, neuroplasticity, neurogenesis and changes in neuroendocrine function. These mechanisms potentially contribute to the different behavioral, mood, and cognitive changes observed after exercise [6]. In order to address the specific neural and behavioral aspects of depression that are reversed by physical activity and the potential mechanisms that may account for these changes, animal models of depression must be employed in order to enhance translatability of the effects of exercise on behavior to clinical populations.

In the current experiment, we examined the effects of exercise on cognitive and locomotor/exploratory behavior in the olfactory bulbectomy (OBX) model of depression and neurological damage, which results in numerous neurobiological and behavioral deficits that resemble key features of human depression and are reversed by several therapeutic interventions including pharmacotherapy and physical activity [7–9]. One major feature of the OBX model is a change in cognitive performance during several tasks, including passive avoidance [10,11], radial maze [12], conditioned place preference [13], radial water maze [14], Morris water maze [15], and the Y-maze task [16]. We were particularly interested in examining the ability of exercise to alter cognitive performance in this model given the ample evidence supporting a beneficial effect of exercise on cognition. In animal models, this effect has been demonstrated in several cognitive tasks including Morris water maze [17–21], radial arm maze [22], passive and active avoidance [23,24], step-down fear conditioning [25], conditioned place preference [26], and the

* Corresponding author. Tel.: +1 503 943 7779; fax: +1 503 943 7784.
E-mail addresses: vanhoomi@up.edu (J. Van Hoomissen), kunrathj@gmail.com (J. Kunrath), reneedent@gmail.com (R. Dentlinger), lafrenz@up.edu (A. Lafrenz), krausema@sou.edu (M. Krause), sharen.azar@gmail.com (A. Azar).
URL: http://www.up.edu (J. Van Hoomissen).
[1] Present address: Department of Psychology, Southern Oregon University, 1250 Siskiyou Boulevard, Ashland, OR 97520, USA.

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Y-maze task [27], yet very little is known about the effect of exercise on cognitive function in animal models of pathology. It is of interest to determine if exercise has similar behavioral effects in animal models of human pathology compared to controls, since previous research has indicated exercise effects on behavior are dependent upon the status of the animal. For example, chronic activity wheel (AW) running in the Huntington's disease transgenic mouse model reduces cognitive deficits in T-maze performance but does not alter performance in wild-type control mice [28]. In addition, previous work from our lab indicates that the effect of exercise on other behaviors, such as masculine copulatory behavior, is indeed different in control animals compared to animal models of mental health disorders [9]. Thus, we were interested in determining if the effect of exercise on cognitive behavior was similar in control and OBX animals, since OBX leads to reduced performance in cognitive tasks that are enhanced by exercise in control animals. Utilizing one specific type of aversively conditioned memory, contextual fear conditioning (CFC), we, and others, have demonstrated that exercise can enhance performance on this task [29–31], possibly indicating an influence of exercise on aversively motivated conditioned behaviors. Despite the evidence of reduced CFC performance in the OBX model [11], the effects of exercise on this behavior in an animal model of depression are unknown, thus limiting the generalizability of the exercise effect to non-control populations.

Animals undergoing CFC associate various cues in the conditioned context with the aversive foot shock presented during conditioning, which results in the display of the conditioned response (freezing) when those cues are again encountered after a delay period [32]. During the testing session of the CFC behavioral protocol, chronic exercise results in increased freezing behavior in animals that have been exposed to both the context (conditioned stimulus) and the aversive foot shock (unconditioned stimulus), but also in animals that have been exposed to the context only and not the foot shock [31]. It is possible that the observed effect of exercise on CFC behavior is not specific to an effect of exercise on the acquisition or recall of conditioned behaviors, but instead reflects a general overall increase in fear-like, or aversively motivated behavior that would be apparent in any context, not necessarily only in the conditioned context. By testing the animals in both a familiar (aversively conditioned) and a novel (non-conditioned) context, examination of the context specificity of the effect could help rule out the possible hypothesis that chronic exercise leads to a general increase in freezing behavior, rather than an increase in a conditioned, learned response.

An additional key behavioral feature of the OBX model includes increased locomotor or exploratory behavior, often described as hyperactivity, which is generally observed in the home cage shortly after surgery [33] and in the open field test [34]. This hyperactivity is often measured by an increase in locomotor behavior (traveling distance) and an increase in exploratory behavior (rearing) when animals are placed in an open field [7,8]. These effects, however, are reversed or attenuated by chronic treatment with antidepressant drugs [35]. Chronic exercise in the form of treadmill training, AW running, and swimming also influence open-field behaviors, such as locomotion and center entries, but the effect of exercise on these behaviors is not consistent across all exercise protocols and open-field behavior measurement methods [36–44]. No data are available to determine if exercise alters the locomotor/exploratory behavior in the OBX model when exposed to both familiar and novel contexts. Utilizing CFC as the cognitive task, and testing animals in both familiar and novel contexts allowed us to examine the influence of exercise on locomotor/exploratory behavior during behavioral testing.

The inclusion of activity wheel running as an independent variable added one additional measurement of locomotor behavior in the OBX model that was not dependent upon exposure to a novel or conditioned environment that normally results in a stress response in the animal. Rats are motivated to run, with voluntary wheel running behavior increasing over time before reaching a plateau and then decreasing during the later stages of the life span [45]. Examining naturally occurring nocturnal wheel running behavior in the OBX model provides evidence of the motivational state of the animal without the introduction of external stressors associated with many behavioral protocols that take place in non-home-cage environments. Because the epidemiological data suggest a bidirectional relationship between depression and physical activity levels [46,47], wheel running behavior in the OBX model represents an added variable to assess the validity of the OBX model as a model of depression.

Alterations in the regulation of the hypothalamic–pituitary–adrenocortical (HPA)-axis have been associated with a number of clinical conditions including depression [48–50], and the ability of physical activity to alter the neuroendocrine response to non-exercise stressors, may represent an additional beneficial effect of exercise [6,51,52]. However, little is known regarding the influence of exercise on HPA-axis activity during or after exposure to a stressor in an animal model of mental health disease with known dysregulated neuroendocrine function, such as the OBX model [53,54], even though chronic exercise influences neuroendocrine function at baseline and in response to specific stressors [55–57]. The CFC protocol utilized in this experiment involved the application of a mild foot shock during the conditioning session and exposure to both novel and aversively conditioned contexts, thus providing a behavioral context in which to examine the effects of exercise on stress responses in the OBX model. Thus, in order to examine this question, and to minimize the stressors present during the behavior testing, we examined the HPA-axis activity by measuring blood CORT levels at the end of the behavioral protocols.

2. Methods

2.1. Animals and experimental design

Male, Long-Evans rats ($n = 71$, 160–180 g) were individually housed in polypropylene cages on a 12-h light–dark schedule (lights on 08:00–20:00) with food and water provided *ad libitum*. Animals were handled daily and the temperature in the environment was maintained at 21 °C. Upon arrival, the animals were given a 14–16-day accommodation period and then randomly assigned into four groups in a 2 (sham surgery [SHAM] vs. olfactory bulbectomy [OBX]) × 2 (sedentary [SED] vs. activity wheel [AW] running) factorial design. An additional home-cage group that did not undergo surgery or behavioral testing was included for use as a comparison group for the hormone assay. All animal care and experimental procedures adhered to guidelines set forth by the NIH Guide for the Care and Use of Laboratory Animals and were approved by the University of Portland Institutional Animal Care and Use Committee.

2.2. Bilateral olfactory bulbectomy (OBX) surgery

After the accommodation period, animals underwent either olfactory bulbectomy or sham surgery. Animals were anesthetized with ketamine (90 mg/kg, i.p., Fort Dodge) and xylazine (10 mg/kg, i.p., Vetus) prior to surgery. A 1-cm rostral–caudal midline incision was made in the skin of the head, and two small burr holes (2 mm in diameter) were drilled into the skull 6 mm rostral of bregma and 1 mm lateral of the midline. The olfactory bulbs were removed using gentle aspiration, and gel foam (Pharmacia) was inserted into the cavity to control bleeding. The incision was closed with nylon sutures, and the animals were injected subcutaneously with banamine (2.5 mg/kg, Vetus) for pain control and 1–3 ml of saline to compensate for blood loss. Animals were placed under a heat lamp until recovery and then returned to their home cage. Except for the removal of the olfactory bulbs, SHAM animals were given the same treatment as OBX animals. The success and validation of the OBX surgeries was verified using two methods: (1) dissection and direct observation of remaining bulb tissue and through (2) measurements of key behavioral variables altered by OBX, namely locomotor/exploratory behavior during CFC testing. Animals in the OBX groups were excluded from the results if they contained olfactory bulb remnants at the end of the experiment that weighed more than 30% of the SHAM animal bulb tissue or if there was physical damage to the frontal cortex.