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Voluntary exercise increases resilience to social defeat stress in Syrian hamsters

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ABSTRACT

Exposure to social stressors can cause profound changes in an individual's well-being and can be an underlying factor in the etiology of a variety of psychopathologies, such as post-traumatic stress disorder (PTSD). In Syrian hamsters, a single social defeat experience results in behavioral changes collectively known as conditioned defeat (CD), and includes an abolishment of territorial aggression and the emergence of high levels of defensive behaviors. In contrast, voluntary exercise has been shown to promote stress resilience and can also have anxiolytic-like effects. Although several studies have investigated the resilience-inducing effects of voluntary exercise after exposure to physical stressors, such as restraint and electric shock, few studies have examined whether exercise can impart resilience in response to ethologically-based stressors, such as social defeat. In Experiment 1, we tested the hypothesis that voluntary exercise can have anxiolytic-like effects in socially defeated hamsters. In the elevated plus maze, the exercise group exhibited a significant reduction in risk assessment, a commonly used index of anxiety, compared to the no-exercise group. In the open-field test, animals in the exercise group exhibited a significant reduction in locomotor behavior and rearing, also an indication of an anxiolytic-like effect of exercise. In Experiment 2, we examined whether exercise can reverse the defeat-induced potentiation of defensive behaviors using the CD model. Socially defeated hamsters in the exercise group exhibited significantly lower levels of defensive/submissive behaviors compared to the no-exercise group upon exposure to the resident aggressor. Taken together, these results are among the first to suggest that voluntary exercise may promote resilience to social defeat stress in Syrian hamsters.

1. Introduction

Social stressors, such as those related to abuse or bullying, are a significant contributor to the etiology of psychiatric illness including major depression, schizophrenia and post-traumatic stress disorder [1–5]. While the majority of investigations have focused on genetic and/or environmental risk factors as well as maladaptive behavioral responses to stressful or traumatic events that make an individual more susceptible to these disorders, surprisingly few have considered factors that make an individual more resilient to these psychopathologies. Indeed, considering that most individuals that experience a traumatic life event do not develop psychopathologies [6,7], understanding factors that can contribute to stress resilience is a critical avenue of research that has been markedly understudied.

One way to examine these resilience factors is to utilize an animal model, such as conditioned defeat (CD), that uses an ethologically relevant, social conflict stressor [8]. Like humans, social conflict in most mammalian species can lead to a host of long-lasting behavioral and physiological changes, especially in the defeated (or subordinate) individual. For example, a socially defeated Syrian hamster will result in increased levels of plasma adrenocorticotrophin (ACTH) and glucocorticoids, while impairing plasma testosterone and immune function [9–11]. Behaviorally, socially defeated animals will exhibit heightened levels of submissive and defensive behaviors and a complete lack of territorial aggression, even when the defeated animal is paired with a smaller, non-aggressive conspecific, a phenomenon we call *Conditioned Defeat* (CD; [8,10–14]). While the use of social defeat models has become increasingly common, there is currently a paucity of data examining the possible link between social stressors and resilience. Indeed, we have consistently observed that up to 30% of socially defeated

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hamsters exhibit none of the behavioral changes associated with social defeat, and instead show increased social behavior and, occasionally, even a re-establishment of territorial aggression (unpublished findings). Importantly, this effect is independent of the level of social defeat incurred by the hamster, indicating that these effects may reflect the inherent individual variations among our subjects. Similar findings of a wide range of individual differences in other species following social defeat stress have also been reported [15].

One possible factor that has been proposed to contribute to stress resilience is voluntary exercise. In humans, it is well-established that exercise can positively affect an individual's well-being by improving overall mood [16], alleviating anxiety [17], and improving cognitive [18] and cardiovascular [19] function. In rodents, free access to a running wheel has been shown to have anxiolytic-like effects in a variety of behavioral models, including the elevated plus maze, open-field apparatus, social interaction test, and the light-dark box [20–24]. For example, Greenwood and colleagues [22] showed that after six weeks of voluntary wheel running, rats exposed to uncontrollable stress (restraint + tail shock) showed a significant reduction in social avoidance compared to sedentary controls. Furthermore, in one of the few studies that have examined the link between voluntary exercise and social stress, Otsuka and colleagues [25] showed that even limited exposure to a running wheel (2 h per day for 12 days) reduced avoidance behavior in socially defeated mice while inducing an increase in food consumption. While these data lend further support for the benefit of voluntary exercise, no studies to date have specifically examined whether free exposure to a running wheel can impart resilience and reduce anxiety-like behaviors by reversing the effects of social defeat in Syrian hamsters.

The overall aim of the present study was to examine the role of voluntary exercise in socially defeated hamsters. Specifically, our hypothesis was that a moderate amount of voluntary exercise will contribute to an anxiolytic-like effect in the elevated plus maze (EPM) and the open field test (OFT) as well as imparting stress resilience by reducing CD-related behaviors in socially defeated hamsters.

2. Materials and methods

2.1. Animals and housing conditions

Experimental subjects ($n = 50$) consisted of adult male Syrian hamsters (*Mesocricetus auratus*; Charles River Laboratories, Wilmington, MA) approximately 12 weeks old and weighing between 110 and 125 g at the time of testing. All subjects were individually housed for 1 week prior to the start of the experiment in a temperature (22° ± 1.5 °C) and humidity-controlled room with free access to food and water and kept on a 14:10 h light:dark cycle (lights out at 10:00 h). Resident aggressors (RA) used for defeat training were older (> 6 mo), singly housed males weighing between 175 and 205 g. All testing occurred during the first three hours of the dark phase of the light/dark cycle in order to minimize circadian variation of the behaviors. Behavioral testing was conducted in one of two dedicated rooms located adjacent to the vivarium. All procedures and protocols were approved by the Morehouse College School of Medicine Institutional Animal Care and Use Committee (IACUC).

2.2. General experimental methods

2.2.1. Running wheel protocol

Subjects were weight matched and assigned to either the exercise (EX; $n = 26$) or no exercise (NEX; $n = 24$) groups. Animals in the EX group was allowed free access to a running wheel in their home cages for 20 consecutive days (Experimental Days 1–20), during which duration of running wheel use was recorded daily by trained observers in the vivarium beginning one hour after lights out using time-sampling, whereby the behavior, in duration, of the subjects was rated every 10-min over a 5-min time period using hand held timers. The duration of wheel running was based on previous research demonstrating that a range between 14 and 21 days was optimal for eliciting anxiolytic-like effects [21], or social avoidance effects [25], two behavioral indices that were examined in the present study. The following behaviors were scored: running wheel use, locomotion outside of the wheel, rearing, grooming and miscellaneous behaviors (eating, drinking, lying down). Observations occurred daily between 11:00 h and 14:00 h under red light. Control animals were placed into cages without a running wheel but had access to a wooden dowel and nestlets to minimize the negative effects of single housing.

2.2.2. Social defeat

On Day 21 of the experiment, all subjects were defeated in the home cage of one of 12 randomly assigned RA's, with each RA paired with the experimental subject an average of 4 times. The social defeat protocol used in the present study was a modified version of the method used by McCann and Huhman [14] and consisted of three 5-min defeats in the home cage of a RA with an inter-trial interval (ITI) of 5 min. While the same RA was used for subjects during the three 5-min defeat sessions, care was taken to ensure that an RA was not used consecutively for the next subject. Following defeat, subjects were immediately returned to their home cage (with or without the running wheel). Latency to first attack and mean duration of aggression were scored live by a trained observer to ensure that all subjects experienced similar levels of defeat. All defeat pairings occurred during the first three hours of the light/dark cycle and was conducted under red light.

2.3. Experiment 1: anxiety test battery

Immediately after social defeat (Experimental Day 21), 13 subjects from the EX group and 12 subjects from the NEX group were randomly selected and tested in the elevated plus maze, followed by the open-field test.

2.3.1. Elevated plus maze

Following defeat, subjects were transported individually to an adjacent room, allowed 3 min to acclimate to the new environment, and placed into the EPM, facing the same closed arm for 5-min. The EPM was constructed out of black acrylic and consisted of two open and two closed arms (50 cm × 10 cm) and elevated 50 cm above the floor. The walls of the closed arms were 30 cm in height. A 0.70 cm rim surrounded the outer edge of the open arm to prevent test subjects from falling off the maze. Mean percentage of duration spent in the open arm over total time spent in both open and closed arms as well as mean frequency of entries into each arm were scored. The following behavioral measures were also scored: frequency of rearing, risk assessment (stretch attend posture, flat back locomote), and head out (the head of the subject extends out from the closed arm of the maze to the central square). Testing was conducted under white light. Trials were recorded on a camcorder, transferred to a computer and behaviors scored by a trained observer using the behavioral analysis software, Hindsight (developed by Scott Weiss, Ph.D., University of Hawaii).

2.3.2. Open-field test

Immediately following the EPM, animals were transferred to an adjacent room, allowed 3-min to acclimate to the new environment and then placed into the open field apparatus for 5-min. The open field consisted of a square box (60 × 60 cm; wall height: 20 cm), constructed of clear acrylic. The floor of the apparatus was divided into 36 10 × 10 cm squares to facilitate analysis of locomotor activity. Latency to exit the outer 20 squares, latency to enter the central 4 squares and percentage of time spent in the central squares were measured. The following behaviors were also measured: locomotor activity (number of lines crossed), rearing and grooming. Testing occurred under white light. Trials were recorded on a CCD video camera connected to a DVD