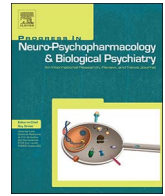




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Prior treadmill exercise promotes resilience to vicarious trauma in rats



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ABSTRACT

Background: Post-traumatic stress disorder (PTSD) is a serious psychological condition, which can develop both from physically experiencing and also from witnessing traumatic events. There is evidence that physical exercise can have a positive impact on the symptoms of PTSD. Relevant to this, in our previous pre-clinical work, beneficial effects of treadmill exercise were reported on PTSD-like behaviors in a social defeat paradigm, a rat model of direct physical trauma. However, the role of exercise on vicariously acquired PTSD-like phenotype was not examined.

Objective: In this study, we utilized a rodent PTSD model, which mimics both the physical as well as the witness experience of trauma, and examined the impact of moderate treadmill exercise in mitigating vicariously acquired PTSD-like behaviors in rats.

Methods: Our PTSD model is a modified social defeat paradigm, which involves aggressive encounters between a large Long-Evans male rat (resident) and a smaller Sprague-Dawley male rat (intruder), resulting in intruder social defeat. The cage mate of the intruder is positioned to witness intruder defeat. Rats were grouped as control (CON), social defeat (SD), exercise (EX), trauma witness (TW), and exercise prior to trauma witness (EX-TW). After acclimatization for 7 days, the exercised groups were subjected to a daily 30-min treadmill exercise regimen for 14 days. On day 21, the SD group was exposed for 7 days of social defeat, while the TW groups witnessed social defeat. On days 28–34, behavioral and cognitive tests including short-term (STM) and long-term (LTM) memory function, anxiety- and depression-like behaviors were conducted.

Results: TW and SD rats demonstrated the highest levels of anxiety- and depression-like behaviors, while EX-TW rats did not exhibit anxiety- and depression-like behaviors. TW and SD rats showed no impairments in STM. However, TW and SD rats showed impairments in LTM, and exercise rescued LTM impairments in EX-TW rats.

Conclusions: This study demonstrates that rats subjected to direct experience or witness of social defeat exhibited PTSD-like behaviors, while moderate treadmill exercise prevented trauma witness-induced behavioral impairments. These studies have important translational value suggesting that prior treadmill exercise might provide resilience to stressful stimuli and perhaps mitigate the witnessing effects of traumatic events.

1. Introduction

Post-traumatic stress disorder (PTSD) is a maladaptive and common psychiatric disorder developed upon exposure to traumatic events. PTSD patients exhibit a broad range of symptoms including hyperarousal, intrusive memories, anxiety, depression and poor cognition (Patki et al., 2013). Interestingly, PTSD can be triggered not only in people who personally experience traumatic events, but also in those who witness it (Zimering et al., 2006). For example, a child who repeatedly witnesses physical and emotional abuse of a parent or sibling can develop PTSD (Lehmann, 1997). The Diagnostic and

Statistical Manual of Mental Disorders has recognized that learning of or witnessing traumatic events experienced by friends or family can contribute to PTSD (A. American Psychiatric and D.S.M.T. Force, 2013). PTSD remains very difficult to treat. Currently, selective serotonin reuptake inhibitors (SSRIs) are the treatment of choice (Schoenfeld et al., 2004). However, their use is controversial due to their frequently reported side effects and poor patient compliance (Penn and Tracy, 2012). Other non-pharmacological interventions, including physical exercise, are attractive side-effect free approaches. Low-to-moderate intensity exercise reportedly elevates mood, reduces anxiety (Shamus and Cohen, 2009) and acts as an overall stress-buffer (Tsatsoulis and

Abbreviations: PTSD, post-traumatic stress disorder; SD, social defeat; TW, trauma witness; Ex, exercise; LD, light/dark test; EPM, elevated plus maze test; STM, short-term memory; LTM, long-term memory; FST, forced swim test

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Fountoulakis, 2006). It is also known to have a positive impact on the symptoms of depression and PTSD (Shamus and Cohen, 2009).

Relevant to this, in our previous pre-clinical work, the beneficial effect of moderate physical exercise was reported on PTSD-like behaviors using two separate stress paradigms, one was a social defeat paradigm (Patki et al., 2014a), and the other was a single prolonged stress (SPS) model (Patki et al., 2014b). Both rat models were based on direct physical trauma. However, the role of physical exercise on vicariously acquired PTSD-like phenotype was not examined. Although animal models cannot accurately reveal the impact of traumatic events on psychiatric symptoms occurring in later life, rodent models are excellent tools that can provide useful insights. In this study, we utilized a rodent PTSD model which mimics both the physical as well as the witness experience of trauma and examined the impact of moderate treadmill exercise on mitigating vicariously acquired PTSD-like behaviors in rats. Rodent treadmill exercise apparatus is a well-suited method for subjecting rats to physical exercise (Salim et al., 2010). Our studies presented herein offer important insights into the role of physical exercise in promoting resilience to trauma witness. This is particularly important and of high translational relevance for designing PTSD-related management and treatment strategies.

2. Methods

2.1. Animal model

Upon arrival at the animal facility, rats were housed on a 12-hr light/dark cycle in a climate-controlled room with food and water provided *ad libitum*. Experiments with rats were conducted in accordance with the NIH guidelines using protocols approved by the University of Houston Animal Care and Use Committee. Male Sprague-Dawley rats (225–250 g) were used as controls or intruders, and male Long-Evans (LE) retired breeders (400–500 g) served as resident aggressors (Charles River, Wilmington, MA).

The social defeat model (Miczek, 1979), involving aggressive encounters between a large LE male rat (resident) and a smaller Sprague-Dawley male rat (intruder) is a well-recognized rodent model of PTSD (Patki et al., 2013; Bhatnagar and Vining, 2003; Bhatnagar et al., 2006; Wood et al., 2010, 2012). In this study, a modified version of the resident-intruder model was used (Patki et al., 2014c). Three Sprague-Dawley rats were housed together during the acclimatization period for 7 days. Later, one Sprague-Dawley rat, considered as an intruder and designated as socially defeated (SD), was introduced into the cage of the resident LE rat. The cage mates of the SD rat were placed in the Plexiglas enclosure surrounding the cage where both LE and SD rats were present (Fig. 1A). The cage mates were considered as the trauma witnessing (TW) rats. Introduction of the SD intruder rat into the cage of the resident LE rat results in social defeat of the intruder rat, indicated by the intruder surrendering, when attacked by the resident LE rat. After defeat, a perforated Plexiglas partition was placed in between the LE and SD rats to avoid injury to the intruder. This partition allowed visual, auditory, and olfactory interactions for the remainder of the 30-min session (Fig. 1A). The TW rat present outside the cage in the enclosure witnesses the social defeat of the SD rat. Two more bouts of social defeat were performed with 5-min separation, in order to reinforce the visual stress in the TW rat. After social defeat sessions, the SD and TW rats were housed together until the next day of social defeat protocol.

2.2. Moderate treadmill exercise

Rats ($n = 70$) were randomly selected into five groups (14 rats/group): control (CON), social defeat (SD), exercise (EX), trauma witness (TW), and exercise prior to trauma witness (EX-TW). The rats in the two exercise groups were subjected to treadmill exercise on a motorized rodent treadmill purchased from Columbus Instruments, Columbus,

OH. The apparatus consisted of a 3-lane animal exerciser utilizing single belt construction with dividing walls suspended over the tread surface (Fig. 1B). The exercising belt is made with special material that facilitates the animals' grip and is easy to clean. The overall dimensions of the treadmill are, 33 cm × 50.8 cm × 50.8 cm and each exercise lane dimension is 43.8 cm × 12 cm × 12.7 cm. All rats in the exercise groups were pre-trained on the treadmill in order for the animals to adapt to the apparatus. Overall, rats were able to run on the treadmill with minimal requirement for external stimuli or manual prodding. A set of three rats were placed on the treadmill in each session. The rats were subjected to a 30-min daily treadmill exercise protocol for a total of 2 weeks: at a speed of 10 m/min for the first week and a speed of 15 m/min for the second week (Patki et al., 2014a). The rats were given a rest period of 5-min after 15-min of exercise. All of the rats had free access to standard rodent chow and water during the entirety of the experiment. After each session, the treadmill was cleaned with 70% ethanol solution, wiped and air dried before the following session.

2.3. General body parameters

Body weight was recorded on days 8 and 35. At the conclusion of the social defeat and trauma witnessing paradigm lasting for 7 days, depression- and anxiety-like behavior tests were conducted as published (Salim et al., 2010; Vollert et al., 2011). Cognitive functions including short-term (STM) and long-term memory (LTM) tests using radial arm water maze (RAWM) paradigm were performed as published (Alhaider et al., 2010a,b; Aleisa et al., 2011). Rats were sacrificed 7 days after the conclusion of the social defeat protocol. The experimental design is summarized in Fig. 1C.

2.4. Anxiety-like behavior tests

First, light/dark test was conducted followed by elevated plus maze and open field tests as previously published (Salim et al., 2010; Vollert et al., 2011).

2.4.1. Light/dark (LD) exploration

The light/dark box consisted of a light and a dark compartment separated by a barrier with a single opening for passage from one compartment to the other. Total time spent in the lit area was recorded by an observer blinded to the treatment (Salim et al., 2010; Vollert et al., 2011).

2.4.2. Elevated plus maze (EPM)

A standard rat elevated plus maze with 43 cm arms extending from a 10 cm central area 90 cm above the floor was used (Med Associates Inc., St. Albans, VT). The rat was placed in the central area facing the open arms of the maze and each session lasted 5-min. The rat's movements were tracked visually by an observer who was blinded to treatment, and the amount of time the rat spent in the open arms was determined (Bert et al., 2002).

2.4.3. Open field (OF) activity

Rats were placed in the center of the OF (60 × 40 cm) and left to explore the arena for 15-min. Total activity, ambulatory activity, and distance covered were determined using a Opto-Varimex Micro Activity Meter v2.00 system (Optomax, Columbus Instruments; OH) as previously published by our lab (Salim et al., 2010; Vollert et al., 2011).

2.5. Depression-like behavior test

2.5.1. Forced swim test (FST)

The FST is a test used for measuring depression-like behavior in rodents (Can et al., 2012). Rats were individually placed in a 24 cm × 50 cm cylinder filled with water (25 °C) for 5-min. At some point after being placed in the water the rat assumes an immobile

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