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Behavioral changes over time in post-traumatic stress disorder: Insights from a rat model of single prolonged stress

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ABSTRACT

Post-traumatic stress disorder (PTSD) is manifested as a persistent mental and emotional condition after potentially life-threatening events. Different animal models of PTSD have been developed for neuropathophysiology and pharmacological evaluations. A single prolonged stress (SPS) induced animal model has demonstrated to result in specific neuro-endocrinological dysregulation, and behavior abnormalities observed in PTSD. However, animal studies of PTSD have mostly been performed at one time point after SPS exposure. To better understand the development of PTSD-like behaviors in the SPS animal model, and to identify an optimal period of study, we examined depressive behavior, anxiety-like behavior, physical activity and body weight in SPS model rats for two weeks. Our results confirmed the SPS-induced PTSD-like behavior and physical activity observed in previous studies, and indicated that the most pronounced symptomatic behavior changes were observed on day 1 and 7 after SPS exposure, which may involve stress-induced acute hormone changes and unclear secondary neurobiological changes, respectively. These results provide a solid basis for further investigation into the neuro-pathophysiology of or neuropharmacology for PTSD using the SPS rat model. However, for chronic (pharmacological) studies longer than 7 days, a prolonged PTSD animal model should be developed, perhaps using enhanced stimulation.

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1. Introduction

Post-traumatic stress disorder (PTSD), first recognized in the third edition of the DSM in 1980 (Kilpatrick et al., 1998), is manifested as a persistent mental and emotional condition after potentially life-threatening events, and is characterized by anxiety, hyper-arousal, generalized fear, intrusive memories, and depressive symptoms (Siegmund and Wotjak, 2006; Yehuda and LeDoux, 2007). Combat, natural disasters, sexual assault and life-threatening accidents can trigger PTSD and other trauma-related syndromes (DiMauro et al., 2014). PTSD can result in interpersonal problems, parenting difficulties and reduction in household income, and is strongly associated with suicidal behavior (Sareen et al., 2011). PTSD also takes a toll on families and the wider society (Rampp et al., 2014). PTSD is one of the most frequently diagnosed psychiatric disorders, occurring in approximately 5% of the general population with a lifetime prevalence of 7–12% (Breslau et al., 1998). While many individuals with PTSD no longer experience symptoms a few years after the traumatic event, 30–40% of the patients experience chronic symptoms (Kessler et al., 1995).

Animal models are useful tools for investigating the neurobiological basis of PTSD, and developing novel therapeutic strategies for PTSD (Serova et al., 2013). Exposing animals to a single prolonged stress (SPS) was first proposed by Liberzon et al. (1997) as a laboratory model for the neurobiological mechanisms involved in PTSD (Kohda et al., 2007). Animals were exposed to multiple stressors such as physical restraint, forced swimming and ether exposure (Eagle et al., 2013; Ganon-Elazar and Akirav, 2012; Liberzon et al., 1997; Yamamoto et al., 2009), which were found to induce pathophysiological and behavioral changes in animal that mimic PTSD in human (Yamamoto et al., 2009), including the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (Liberzon et al., 1997), an exaggerated acoustic startle response, which is similar to the

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increased arousal reported in PTSD patients (Khan and Liberzon, 2004), and the increased immobilization time (Ji et al., 2014). More recent animal models of SPS were made more sophisticated by including time-dependent sensitization and exposing animals to a second stressful episode after sensitization (stress-restress) (Cohen et al., 2014).

While studies by using SPS animals have revealed promising insights into the neuro-biological basis of PTSD, some of these results were limited by assessing animals at only at a single time point, which provides little information about the developmental pathology of PTSD (Cui et al., 2008; Iwamoto et al., 2007). Selecting the appropriate time to perform assessment of animals after SPS is an important decision, since certain biological activities occur only at specific times after the exposure. Previous studies have shown that plasma levels of corticosterone dropped quickly and recovered after an initial increase within a week of SPS (Kohda et al., 2007). SPS-induced expression of the apoptotic messengers caspase-9 and caspase-3, which peaked at day 7 (Li et al., 2010). However, how animal behavior changes over time after SPS exposure remains unclear, especially during the early stages. Assessing animal behavior over a longer period of time could provide valuable information about the pathological mechanisms of SPS, revealing the development of PTSD-like symptoms. Therefore, in this study, we examined the temporal pattern of behavioral changes in a PTSD animal model after SPS exposure between day 1 and 14.

2. Methods

2.1. Animals

Male Wistar rats (180 ± 10 g) were purchased from Beijing SPF Vital Laboratory Animal Technology Company (Beijing, China), and were housed in groups of six per cage with ad libitum access to food and water throughout the study. Animals were maintained under a 12-h light/dark cycle (light on from 08:00 to 20:00) at 23 ± 1 °C and 45% relative humidity. The Rats were allowed to acclimate to a colony room for at least 3 days prior to the start of experiments.

A total of 96 male Wistar rats were randomly divided into two groups. One group was treated with SPS exposure, and the other group underwent a control protocol. The PTSD-like behaviors of four animals in each group was assessed at day 1, 4, 7, and 14 after the treatment, and animals were sacrificed after the behavior tests. All rats were weighted immediately before control or SPS treatment, and then once daily for 14 days until sacrifice.

The experiments were approved by the Institutional Animal Ethics Committee of Beijing University of Chinese Medicine.

2.2. Single prolonged stress (SPS)

The rats were subjected to stress in three stages: restraint for 2 h, forced swimming for 20 min, and anesthesia with diethyl ether.

The restraint was conducted in a transparent polyethylene cylindrical tube (diameter, 7 cm; height, 25 cm). One side of the tube was completely sealed with only a breathing hole to allow the rats to breathe freely, and the other side was closed with a cover that could be adjusted to the base of the tail, allowing it to protrude from the cover. The tube size was adjusted according to each rat size in order to immobilize the rat completely. In the forced swimming session, the rats were placed alone in a plastic cage (length, 50 cm; width, 50 cm; height, 25 cm) filled to three fourths full with 25 °C water. After this session, the rats were allowed to recover for 20 min prior to anesthesia, which was performed by placing the rats in a closed box filled with evaporated diethyl ether until they lost consciousness. The rats were then immediately removed from the anesthesia box and returned to the home cages. The control rats remained in their home cages without handling. 1, 4, 7 or 14 days later, the behavioral tests were performed with the rats according to their assigned group prior to sacrifice. The behavior tests included an open field test (OFT), and a forced swimming test (FST) performed within an interval of 24 h after OFT.

2.3. Open field test (OFT)

The rats were tested in an open field under dim light. Briefly, each individual rat was placed in the center of a wooden box (100 × 100 × 40 cm), the bottom area was marked with a grid and equally divided into 25 sectors. Rats were allowed to explore the environment for 5 min prior to behavior recording for another 5 min. The time spent in the central arena (60 × 60 cm) was used to reflect anxiety-like behavior. Total distance traveled was used to reflect general locomotor activity. Other measures included the number of crossings, which was defined as a rat crossing sector boundaries with four paws; maximum distance traveled during an uninterrupted run; mean velocity; vertical activity; number of defecations; and total time spent grooming, which was defined as the time in which a rat stopped running and started licking, chewing and scratching its fur (Jalewa et al., 2014). All the behavioral measures were assessed using EthoVision XT software (Nodule, Netherland). Each rat was tested once only. The arena was thoroughly cleaned with 75% ethanol between tests.

2.4. Forced swimming test (FST)

The rats were individually placed in a water tank (length, 50 cm; width, 50 cm; height, 25 cm) three fourths full with warm water at 25 °C, and left for 5 min. After being placed in the water, the rats became immobile and remained in the water without struggling, making only those movements necessary to keep its head above the water (Cryan and Holmes, 2005). The amount of the time that the rat spent immobile in forced swim session was used to measure depression-like behavior (Borsini and Meli, 1988; Calvo et al., 2011). After this test, the rats were immediately sacrificed.

2.5. Statistical analysis

The results were expressed as mean ± SD. The differences between the results of the SPS and control groups over time were analyzed with two-way ANOVA followed by a post-hoc test using the Holm–Sidak method, in which SPS or control treatment and detection time after treatment were the main effects. Statistical analysis was performed using SigmaStat (version 3.5, Systat software, San Jose, California, USA). A P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Effects of SPS on open field test (OFT) performance

In the OFT test, the SPS stress-induced anxious post-traumatic behavior of animal was evaluated in eight distinct measures. The data was analyzed with two-way ANOVA using treatments, which was SPS exposure or control treatment, and time of detection after treatment as the two main effects. When a significant interaction between treatment and time was detected, a post-hoc test with Holm–Sidak method was used to further analyze the difference between SPS and control group at each detection time point.

a Increased time spent away from the central arena is considered to be the main indication of anxiety in the OFT. We found that overall the SPS rats spent significantly less time (6.23 ± 3.95 s, n = 32) than the control rats (8.76 ± 6.02 s, n = 44) in

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