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Research report

Long-term effects of early adolescent stress: dysregulation of hypothalamic–pituitary–adrenal axis and central corticotropin releasing factor receptor 1 expression in adult male rats

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HIGHLIGHTS

- Adolescent stress induced anxiety- and depression-like behaviors in adulthood.
- Adolescent stress induced spatial memory damage in adulthood.
- Adolescent stress changed HPA function and central CRFR1 expression in adulthood.
- Treadmill exercise prevented behavioral abnormalities.
- Treadmill exercise alleviated HPA axis dysregulation.

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ABSTRACT

Post-traumatic stress disorder (PTSD) is a stress-related mental disorder caused by traumatic experiences. Studies have found that exposure to early stressful events is a risk factor for developing PTSD. However, a limited number of studies have explored the effects of traumatic stress in early adolescence on behavior, hypothalamic–pituitary–adrenal (HPA) axis function, central corticotropin releasing factor receptor 1 (CRFR1) expression and the relative vulnerability of PTSD in adulthood. The current study aims to explore these issues using inescapable electric foot shock to induce a PTSD model in early adolescent rats. Meanwhile, running on a treadmill for six weeks and administration of the antagonist with 3.2 mg/kg/day of CP-154, 526 for 14 consecutive days were used as therapeutic measures. Presently, the stress (S) group showed more anxiety and depression in the open field (OF) test and elevated plus maze (EPM) test, memory damage in the Y maze test, decreased basal CORT level, increased DEX negative feedback inhibition and exacerbated and longer-lasting reaction to CRH challenge in the DEX/CRH test compared with the control group. Central CRFR1 expression was also changed in the S group, as evidenced by the increased CRFR1 expression in the hypothalamus, amygdala and the prefrontal cortex (PFC). However, treadmill exercise alleviated early adolescent stress-induced behavior abnormalities and improved the functional state of the HPA axis, performing a more powerful effect than the CRFR1 antagonist CP-154, 526. Additionally, this study revealed that the alteration of central CRFR1 expression might play an important role in etiology of PTSD in adulthood.

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1. Introduction

Post-traumatic stress disorder (PTSD) is a stress-related mental disorder caused by traumatic experiences. It is well known that dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis is the key factor in etiology of PTSD because activation of the HPA axis is the most important endocrine component of the stress response and its abnormal activities result in neurotransmitter dysfunction and behavioral disorders [1–5]. Neuroendocrine studies have found that there were some significant alterations in HPA axis function in PTSD, which are mainly displayed by enhanced glucocorticoid receptor feedback inhibition [6] and hypothalamic overdrive [7]. To check the CRH receptor sensitivity, ACTH and cortisol response triggered by exogenous CRH was measured. However, there were conflicting results, as one study displayed an exaggerated response [8], one study displayed an attenuated response [9], and another

Abbreviations: PTSD, post-traumatic stress disorder; HPA, hypothalamic–pituitary–adrenal; CRF, corticotropin releasing factor; CRH, corticotropin releasing hormone; CRFR1, corticotropin releasing factor receptor 1; PFC, prefrontal cortex; EPM, elevated plus maze; OF, Open field; DEX, dexamethasone; CORT, corticosterone; SEM, standard error of the mean; CUMS, chronic unpredictable mild stress.

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study showed a normal response [10]. Therefore, there were inconclusive results about the HPA axis functions when considering both the heterogeneity of PTSD and regulation of the HPA axis [2].

Most studies suggested that excessive corticotropin releasing factor (CRF) activity or greater responsiveness of corticotropin releasing hormone (CRH) to stressors was involved in the pathophysiology of PTSD [11]. Therefore, as the key upstream factors in HPA axis activation and regulation, CRF and CRF receptors play a significant role in HPA axis dysfunction involved in anxiety, depression and PTSD pathogenesis [12–14]. It was suggested that modulation of CRF receptors' expression and function in early life may be a persistent and important factor in neuronal dysfunction throughout the lifetime [60], which could increase susceptibility to stress-related disease in adulthood. Therefore, CRF receptors were considered as a potential therapeutic target for stress-related mental disorders. CRFR1 antagonist (for instance, CP-154, 526) displays antidepressant-like effects in the learned helplessness animal model [15]. Moreover, acute administration of CRFR1 antagonist CP-154, 526 or its analog inhibits stress and CRF-induced plasma adrenocorticotropin (ACTH) rising and exhibits an anxiolytic effect [16–18], whereas chronic administration of low doses of CP-154, 526 greatly attenuated defensive withdrawal behavior and made serum corticosterone concentration return to baseline level more quickly after airpuff startle [19]. Based on the findings described above, it has been hypothesized that antagonism of CRFR1 may provide an effective pharmacological treatment for stress-related mental disorders [20].

Several studies have found that exposure to early life stress is a risk factor for developing PTSD. A meta-analysis concluded that individuals who had been exposed to prior trauma were more likely to develop PTSD than individuals who had not been exposed to prior trauma [21]. A recent study analyzed the data from 34,653 samples and concluded that high levels of childhood adversity might represent a predisposing factor for multiple mental disorders that persist throughout a lifetime [61]. Moreover, a cross-sectional survey confirmed that prior direct exposure to or witnessing violence and forced sexual acts were predictors of post-traumatic stress reactions in adolescents after the Oslo Terror events of 2011 [22]. Additionally, evidence from rodent and primate models also indicated that early-life stress such as maternal separation, abuse and social deprivation could induce persistent emotional and behavioral disorders [23] and HPA axis suppression [24]. A complex, long-term dysfunction of both basal cortisol levels and HPA response to stressors, observed in child maltreatment (reviewed by [1]), indicated that the effect of early-life stress on HPA function and the role in etiology in PTSD should be further studied. Adolescence is a special period of neurobiological and behavioral development, in which period-prominent developmental transitions are observed in the limbic brain regions and prefrontal cortex [25]. A limited number of studies, however, have explored the influence of traumatic stress in early adolescence on HPA function and central CRFR1 expression, and their relative vulnerability to PTSD in adulthood.

As a potential non-pharmacological therapeutic approach, regular exercise has considerable beneficial effects on brain function and plasticity, as observed in many studies. Moderate physical exercise ameliorates single-prolonged stress (SPS)-induced behavioral deficits in rats [26], enhances spatial learning in aged rats [27] and reverses stress-induced alterations in rat hippocampal synapses, mediating antidepressant actions [28]. This extensive evidence indicates that exercise may be beneficial in improving PTSD-induced symptoms including anxiety-like behavior, depressive behavior, and learning and memory impairment [5].

In the present study, inescapable electric foot shock was used to induce a PTSD model in early adolescent rats, which replicates the specific neuroendocrinological abnormalities observed in PTSD patients [29]. We then considered long-term regular exercise as a potential non-pharmacological therapeutic approach to treat the animals following PTSD induction compared with chronic administration of CRFR1 antagonist CP-154, 526. Open field test and elevated plus maze were used to check the anxiety-like and depression-like behavior; Y maze test was used to check the spatial memory; DEX/CRH test was used to detect the functional state of the HPA axis; and immunohistochemistry and western blotting were used to detect the central CRFR1 expression in this study. Thus, the purpose of the present study was as follows. First, we wanted to investigate the long-term effects of early adolescent traumatic stress on anxiety-like behavior, depression-like behavior, memory damage, dysregulation of HPA axis function and central CRFR1 expression in adulthood. Second, we urgently want to reveal whether the anxiolytic effect, antidepressant-like effect, improvement of memory and HPA axis function were observed after long-term regular treadmill exercise, compared with chronic administration of CP-154, 526. Moreover, does long-term regular treadmill exercise and chronic administration of CP-154, 526 lead to adaptive alterations in central CRFR1 expression?

2. Material and methods

2.1. Animals

A total of 64 male Wistar rats (21 days old, obtained from the experimental animal center of Shandong University, China) were group-caged (two or three per cage) under controlled temperatures ($25 \pm 2\,^{\circ}C$) and lighting conditions (07:00–19:00 h) with food and water made available ad libitum, and allowed to acclimate for seven days prior to experimental testing. The study was approved by the Institutional Animal Care Committee of Shandong University.

2.2. Animal model of PTSD

Rats were randomly divided into four groups (n = 16 in each group): the control group (CON), the stress group (S), the stress and exercise group (S + E), and the stress and antagonist group (S + A). With the exception of the control group, the rats in other groups received the repeated inescapable electric foot shock, according to the previously published method [29]. The animals received 0.5 mA of electric foot shock for six consecutive days. Electric foot shock continued for 6 s, repeated 20 times with a random interval in a 30-min period in each trial, with two trials per day. The interval between the two trials was not less than 4 h.

2.3. Treadmill exercise protocol

The long-term regular exercise protocols were modified from a previously published method [30]. The rats were forced to run on the treadmill with a gentle encouragement by a human operator using a tongue depressor at the beginning. Most rats will spontaneously run on a treadmill when they are familiar with the environment due to their vivacious nature. The rats in the S + E group ran on a motorized treadmill for five days/week, for six weeks, starting one day after the last electric foot shock. The rats ran on a treadmill which was partitioned into six channels ($90 \times 10 \times 20\,cm^3$ for each channel) at an intensity of ~70% of the animal's maximal oxygen consumption. In the first week, the rats ran at a speed of 9 m/min, 10 min/day. In the subsequent five weeks, the running time was eventually extended to 60 min/day on the 6th week. The training loads were modulated according to the newly determined peak oxygen consumption of the rats every two weeks. The training loads on the 1st, 3rd and 5th week were 9, 12 and 15 m/min, respectively. When the rats were put into a treadmill channel, the trainer turned on the power switch to encourage them

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