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Resveratrol ameliorated the behavioral deficits in a mouse model of post-traumatic stress disorder

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ABSTRACT

Post-traumatic stress disorder (PTSD) has become a major psychiatric and neurological issue. Resveratrol is shown to be effective on depression and anxiety. However, the mechanism of anti-PTSD-like effects of resveratrol remains unknown. The present study aimed to explore the possible molecular and cellular mechanisms underlying the anti-PTSD-like effects of resveratrol. Following a 2-day exposure to inescapable electric foot shocks, animals were administered resveratrol (10, 20, and 40 mg/kg, i.g.) during the behavioral tests, which included contextual freezing measurement, elevated plus maze test, staircase test, and open field test. Similar to the positive control drug sertraline (15 mg/kg, i.g.), the behavioral deficits of stressed mice were blocked by resveratrol (20 and 40 mg/kg, i.g.), which reversed the increased freezing time in contextual freezing measurement and the number of rears in the staircase test and blocked the decrease in time and number of entries in open arms in the elevated plus maze test without affecting the locomotor activity in the open field test. In addition, resveratrol (20 and 40 mg/kg, i.g.) antagonized the decrease in the levels of progesterone and allopregnanolone in the prefrontal cortex and hippocampus. Furthermore, long-term resveratrol attenuated the dysfunctions of hypothalamic-pituitary-adrenal axis simultaneously. Collectively, the evidence indicated that the anti-PTSD-like effects of resveratrol were associated with the normalization of biosynthesis of neurosteroids in the brain and prevention of the hypothalamic-pituitary-adrenal axis dysfunction.

1. Introduction

Post-traumatic stress disorder (PTSD) is a frequently chronic and disabling condition that is categorized as a trauma- and stressor-related disorder by the diagnostic and statistical manual of mental disorders (Contractor et al., 2017). Lifetime prevalence rates of PTSD range between 6.4% and 7.8% in the general population (Lis-Turlejska et al., 2016) and approximately 20% among combat-exposed military veterans (Breyer et al., 2014). Selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline and paroxetine) are the usual treatment options for PTSD (Bernardy and Friedman, 2015). However, SSRIs have their limitations, such as delayed onset of action, response or non-response with residual symptoms, and other severe side effects (Zhang et al., 2016). Thus, discovery of the novel anti-PTSD drugs is needed.

Traditional Chinese medicine draws more attention in this area and provides a prospective alternative to the treatment of PTSD (Qiu et al., 2015; Wang et al., 2009). Resveratrol, which is found in a wide range of foods such as red wine and grapes, is a naturally occurring polyphenolic compound that is widely present in various plants, such as grapevines, peanuts, and pomegranates (Liu et al., 2016). Resveratrol has been shown to possess a wide spectrum of pharmacologic properties, including anti-diabetic, anti-oxidant, anti-tumor, anti-inflammatory, lipid-lowering properties (Pang et al., 2015). In neurological studies, resveratrol elicited antidepressant- and anxiolytic-like effects in various animal models (Ali et al., 2015; Magaji et al., 2017). These observations have led to the hypothesis that resveratrol may be effective in attenuating stress-induced psychiatric conditions, including PTSD. However, the anti-PTSD-like effects of resveratrol remain unclear. The present study aimed to explore these effects through a classical rodent model.

Furthermore, it is essential to investigate the anti-PTSD-like

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mechanisms of resveratrol. Studies have also been conducted to explore factors and reliable biological markers of PTSD. Research underlying the neurobiology of PTSD is associated with various neuroendocrine systems, such as dysregulation of the hypothalamic-pituitary-adrenal axis and biosynthesis of neurosteroids (Fenchel et al., 2015; Pinna and Rasmusson, 2012). Enhanced negative feedback inhibition of the hypothalamic-pituitary-adrenal axis may be a risk factor for PTSD. The levels of hypothalamic-pituitary-adrenal stress hormones, such as corticosterone, corticotropin-releasing hormone, and adrenocorticotropic hormone, have been shown to be closely associated with PTSD pathology (Golier et al., 2007; Jin et al., 2016). These stress hormones are responsible for the release of glucocorticoids and are elevated in animal models or patients with PTSD (Raglan et al., 2017).

In addition, studies show that altered levels of allopregnanolone are associated with PTSD symptoms (Möller et al., 2016; Qiu et al., 2015). Decreased biosynthesis of this neurosteroid has been implicated as one of the possible factors for PTSD development (Pinna, 2014). The levels of neurosteroids are lowered in patients with PTSD and contribute to the dysfunction of excitatory neurotransmission, leading to PTSD symptoms (Pinna and Rasmusson, 2012). Neuroactive steroids (such as progesterone and allopregnanolone) have been shown to induce anti-PTSD-like activities. For instance, normalization of allopregnanolone levels in brain may induce the anti-PTSD-like profile of drug treatments (e.g., AC-5216, YL-IPA08 and sertraline) in rodents (Zhang et al., 2014, 2016).

The present study evaluated the effects of resveratrol on PTSD-like effects by adapting the inescapable electric foot shock model in mice. The animal model is practical because it mimics the role of prior traumatic experiences in predicting subsequent dysfunction (Jin et al., 2016; Qiu et al., 2013). Following the exposure to foot shocks, the animals were subjected to various behavioral tests such as contextual freezing measurement, elevated plus maze test, staircase test, and open field test. To further investigate the possible molecular and cellular mechanisms underlying the anti-PTSD-like effects of resveratrol, we studied the biosynthesis of neurosteroids in the brain and the hypothalamic-pituitary-adrenal axis activation after chronic resveratrol treatment.

2. Materials and methods

2.1. Drugs and reagents

Resveratrol (purity ≧ 95.0%) and sertraline were obtained from Sigma-Aldrich (St Louis, MO, U.S.A.). Sertraline (15 mg/kg, i.g.) was administered as a positive control on the basis of the previous PTSD studies (Qiu et al., 2013; Zhang et al., 2012). Both drugs were prepared in physiological saline and administered to mice by gavage at a volume of 10 mL/kg. Sertraline and resveratrol (at doses of 10, 20, and 40 mg/kg i.g.) were given once daily for 17 days (from days 3 through 19 between 8:00 and 9:00 am) following the footshock procedures (Fig. 1). The drug administration regimen was based on the chronic drug treatment regimen for this model (Li et al., 2006; Zhang et al., 2012). The doses of resveratrol were based on its antidepressant- and anxiolytic-like effects (Ge et al., 2016; Pang et al., 2015). All the behavioral tests were performed 1 h after drug administration. Control animals received physiological saline.

2.2. Animals

ICR mice (male, 20 ± 2 g, 7 weeks) were purchased from the Vital River Laboratory Animal Technology Company (China). The animals were maintained under controlled temperature (23 ± 1 °C), humidity (45–50%), and lighting (12 h/day). The mice were housed in a 12-h light/dark cycle starting at least 5 days before the training session for aversive procedure with ad libitum access to water and food. The experiments were conducted according to the National Institute of Health Guide for the Care and Use of Laboratory Animals (Publications No. 80-23, revised 1996). All efforts were made to minimize animal suffering and reduce the number of animals used.

2.3. Training session for the aversive procedure

The electric foot shock procedure was conducted as described previously, with minor modifications (Qiu et al., 2013; Jin et al., 2016). Briefly, after acclimatization, a Plexiglas chamber with a stainless steel grid floor was used for the training session. Electric foot shocks were delivered through the grid floor using an isolated shock generator. Each mouse was placed in the chamber, and after a 5-min adaptation period, a total of 15 intermittent, inescapable foot shocks (intensity: 0.9 mA, interval: 8 s, and duration: 10 s) were delivered. The rats were exposed to the same foot shock section for two consecutive days (day 1 and 2). Control animals were placed in the same chamber without electric foot shocks.

2.4. Behavioral paradigms

After the mice were exposed to the electric foot shock procedure, behavioral assessments, namely contextual freezing measurement (on day 7, 11, and 19), elevated plus maze test (on day 13), staircase test (on day 15), and open field test (on day 17), were performed on different days. The schedule of the behavioral tests and drug treatments is outlined in Fig. 1.

2.5. Contextual freezing measurement

The contextual freezing measurement is based on a previous study that the freezing response on re-exposure to the shock context is an indication of conditioned fear memory (Zhang et al., 2016). The test was performed as described previously (Qiu et al., 2013; Zhang et al., 2014). Mice were exposed to reminders of the situation for 5 min on day 7, 11, and 19 without foot shocks to measure the duration of contextual freezing behavior. This was achieved by placing the animals in a chamber identical to the one where the foot shocks were delivered previously. Freezing behavior was defined as total absence of body or

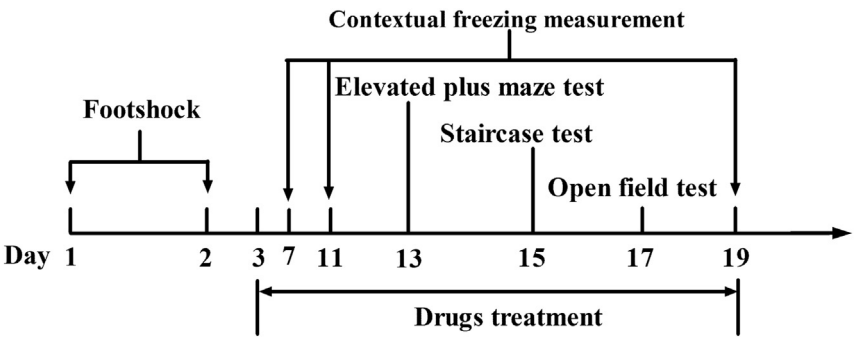

Fig. 1. Treatment schedule and order of behavioral tests for the inescapable electric foot shock model in mice. The drugs or vehicle were injected once daily (i.g.) from days 3 to 19 and 1 h before each behavioral test. After exposure to foot shocks, animals were subjected to different behavioral tests: contextual freezing measurement (on day 7, 11, and 19), elevated plus maze test (on day 13), staircase test (on day 15), and open field test (on day 17).

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