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Research article

WY-14643, a selective agonist of peroxisome proliferator-activated receptor-α, ameliorates lipopolysaccharide-induced depressive-like behaviors by preventing neuroinflammation and oxido-nitrosative stress in mice

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ABSTRACT

Depression is a common disease that afflicts one in six people at some points in life. Numerous hypotheses have been raised in past years, but the exact mechanism that can be used to explain the development of depression remains obscure. Recently, more and more attentions are being focused on neuroinflammation and oxidative stress in depression. WY-14643, an agonist of peroxisome proliferator-activated receptor-α (PPAR-α), has been reported to inhibit neuroinflammation and oxidative stress, and one of our previous studies have showed that WY-14643 possesses antidepressive activities. On that account, we investigated the effect of WY-14643 pretreatment on lipopolysaccharide (LPS)-induced depressive-like behaviors, neuroinflammation and oxido-nitrosative stress in mice. Results showed that WY-14643 pretreatment at the doses of 5 and 10 mg/kg significantly ameliorated LPS (0.83 mg/kg)-induced depressive-like behaviors in the tail suspension test (TST), forced swimming test (FST) and sucrose preference experiment. Further analysis showed that WY-14643 pretreatment not only inhibited the production of pro-inflammatory cytokines induced by LPS, such as interleukin-6 (IL-6), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), but also prevented the LPS-induced enhancement of oxidative and nitrosative stress in the hippocampus and prefrontal cortex. In addition, the LPS-induced decreases in hippocampal and prefrontal cortical brain-derived neurotrophic factor (BDNF) levels were reversed by WY-14643 pretreatment. Taken together, our data provide further evidence to show that WY-14643 could be an agent that can be used to treat depression, and inhibition of neuroinflammation and oxido-nitrosative stress may be the potential mechanism for the antidepressive effect of WY-14643.

1. Introduction

Numerous studies have reported that overactivation of neuroinflammation and oxido-nitrosative stress plays important roles in the formation and/or development of major depression (Cazareth et al., 2014 and Rodrigues et al., 2014). For example, immunologic challenge of animals with lipopolysacchride (LPS) can trigger the occurrence of depressive symptoms via increasing the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) (Liu et al., 2014 and Dobos et al., 2012). The levels of these cytokines have also been found to be increased in depressive patients (Lees et al., 2015 and Bai et al., 2015). Mechanistically, these pro-inflammatory cytokines have been reported to mediate the development of depression through generation of oxido-nitrosative stress (Sulakhiya et al., 2014 and Jangra et al., 2016) and impairment of brain-derived neurotrophic factor (BDNF) expression (Calabrese et al., 2014). Intervening in the process of neuroinflammation along with oxido-nitrosative stress may be beneficial for the therapy of major depression.

WY-14643 is identified as a selective agonist of peroxisome proliferator-activated receptor-α (PPAR-α), one of the three subtypes of the nuclear receptor PPAR family (Puligheddu et al., 2013 and Pontis et al., 2016). Recently, more and more of WY-14643-mediated inflammation-regulating effects are being reported. For example, WY-

Abbreviations: ANOVA, analysis of variance; BDNF, brain derived neurotrophic factor; CSDS, chronic social defeat stress; DMSO, dimethyl sulfoxide; FST, forced swimming test; GSH, glutathione; IL-1β, interleukin-1β; IL-6, interleukin-6; LPS, lipopolysaccharide; MDA, malondialdehyde; NO, nitric oxide; OFT, open field test; PPAR-α, peroxisome proliferator-activated receptor-α; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; TST, tail suspension test.

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14643 has been reported to decrease inflammatory markers in experimental periodontitis (Briguglio et al., 2010). Activation of PPAR-α by WY-14643 inhibits LPS-induced inflammation in synovial fibroblasts (Cheng et al., 2004) and protects cortical neurons from pro-inflammatory mediators-induced cell injuries (Gray et al., 2011). WY-14643 can also exhibit inhibitory effects on pro-inflammatory responses in microglia (Wang and Namura, 2011 and Kim et al., 2002). Furthermore, WY-14643 has been widely reported to ameliorate oxido-nitrosative stress in disease models. For instance, WY-14643 has been shown to ameliorate perfluorododecanoic acid-induced production of reactive oxygen species in rat liver (Liu et al., 2016). Activation of PPAR-α by WY-14643 protects against endoplasmic reticulum stress-induced HepG2 cell apoptosis (Tang et al., 2014). In the brain, WY-14643 can attenuate the generation of reactive oxygen species (ROS), nitric oxide (NO) and lipid peroxidation end-products induced by transient cerebral ischemia/reperfusion, and reverse the ischemia/reperfusion-induced decrease in endogenous antioxidant glutathiones (Collino et al., 2006). Based on these backgrounds, we supposed that WY-14643 administration may result in protective effects against LPS-induced depressive-like behaviors in mice. This hypothesis was evaluated by measuring the alteration of IL-6, IL-1β and TNF-α levels, along with changes in oxido-nitrosative stress parameters in brain areas of hippocampus and prefrontal cortex following an immune challenge with LPS.

2. Experimental procedure

2.1. Chemicals

Lipopolysaccharide (*Escherichia coli* 0111:B4) was purchased from Santa Cruz (Saint Louis, MO, USA). WY-14643, fluoxetine and L-Reduced glutathione were the products of Sigma (St. Louis, MO, USA). IL-1β, IL-6 and TNF-α immunoassay kits were purchased from Invitrogen Co. (Carlsbad, CA, USA). The BDNF measurement ELISA kit was purchased from Promega (Madison, WI, USA). All other chemicals were of analytical grade and purchased from Sigma unless mentioned otherwise.

2.2. Animals

8–10 weeks old male ICR mice were housed five per cage under standard conditions (12-h light/dark cycle; lights on from 07:00 to 19:00; 23 ± 1 °C ambient temperature; 55 ± 10% relative humidity) for 1 week with free access to food and water. Each experimental group consisted of 12 mice. Behavioral experiments were carried out between 9:00 and 11:00 a.m. to avoid circadian variation.

2.3. Experimental design

All animals were divided into eight groups ($n = 10$/group) for behavioral and biochemical assessment: (1) group I (control group) was treated with vehicle [Dimethyl sulfoxide (DMSO):PBS (1:1)] of WY-14643 for 7 consecutive days, and then treated with saline 30 min after the last vehicle injection; (2) group II, III and IV were treated with 20 mg/kg of fluoxetine [Dimethyl sulfoxide (DMSO):PBS (1:1)], 5 mg/kg of WY-14643 and 10 mg/kg of WY-14643 for 7 consecutive days, respectively, and then treated with saline 30 min after the last drug injection; (3) group V (LPS control group) was treated with vehicle [DMSO:PBS (1:1)] of WY-14643 for 7 consecutive days, and then treated with LPS (0.83 mg/kg) 30 min after the last vehicle injection; (4) group VI was treated with 20 mg/kg of fluoxetine for 7 consecutive days, and then treated with LPS (0.83 mg/kg) 30 min after the last fluoxetine injection; (5) group VII was treated with 5 mg/kg of WY-14643 for 7 consecutive days, and then treated with LPS (0.83 mg/kg) 30 min after the last WY-14643 injection; (6) group VIII was treated with 10 mg/kg of WY-14643 for 7 consecutive days, and then treated with LPS (0.83 mg/kg) 30 min after the last WY-14643 injection. Behavioral parameters, the forced swimming test (FST) and the open field test (OFT) were assessed after 24 h of LPS treatment. The tail suspension test (TST) was performed after 30 h of LPS treatment. Sucrose preference experiment was conducted after 48 h of LPS treatment. The dosage of LPS inducing depressive symptoms was widely used in previous studies (Sulakhiya et al., 2014; Martin et al., 2014 and Walker et al., 2013). WY-14643, fluoxetine and LPS were administered intraperitoneally (i.p.) in a volume of 5 mL/kg.

2.4. TST

The TST was performed according to the method described by Steru et al. (1985). Briefly, the mice were individually suspended 50 cm above the floor for 6 min by adhesive tape placed approximately 1 cm from the tip of the tail. The duration of immobility was recorded during the last 4 min by an investigator blind to the study. The mice were considered immobile only when they hung passively and were completely motionless, and any mice that did climb their tails were removed from the experiment.

2.5. FST

The FST was performed according to the method of Porsolt et al. (1977). Briefly, the mice were individually placed in a clear glass cylinder (height 25 cm, diameter 10 cm) filled to 10 cm with water at 25 ± 1 °C for 6 min. The duration of immobility was recorded during the last 4 min by an investigator blind to the study. The immobile time was defined as the time spent by the mouse floating in the water without struggling and making only those movements necessary to keep its head above the water.

2.6. Sucrose preference experiment

In this experiment, the mice were given the choice to drink from two bottles in individual cages, one with 1% sucrose solution and the other with water (Mourlon et al., 2010). All mice were acclimatized for 2 days to two-bottle choice conditions, and the position of two bottles was changed every 6 h to prevent possible effects of side preference in drinking behavior. Then, the mice were deprived of food and water for 24 h. On the testing day, animals were exposed to pre-weighed bottles for 1 h with their position interchanged. Sucrose preference was calculated as a percentage of the consumed sucrose solution relative to the total amount of liquid intake.

2.7. OFT

The OFT was performed according to a previous study (Muller et al., 2009). The mice spontaneous locomotor activity was evaluated in the open-field paradigm over a 5-min period. Briefly, the experimental mice were placed individually in the middle of an open-field apparatus (height 40 cm, width 100 cm, length 100 cm) with 25 (5 × 5 cm) squares delineated on the floor. The apparatus was illuminated with a red bulb (50 W) on the ceiling. 30 min after drug injection, mice were placed in the central sector. The squares that each mouse crossed were counted over a 5-min period under dim light conditions by an investigator blind to the study. The open-field apparatus was thoroughly cleaned after each trial.

2.8. Biochemical studies

2.8.1. Preparation of brain homogenate

The experimental mice were killed by cervical dislocation after 24 h of LPS treatment. The mice hippocampus and prefrontal cortex were immediately dissected out and homogenized (10% *w*/*v*) in 0.1 M phosphate buffer (pH 7.4) for further analysis.