



Methyl jasmonate attenuated lipopolysaccharide-induced depressive-like behaviour in mice



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ABSTRACT

Depression is a recurrent neuropsychiatric disorder that affects millions of individuals worldwide and impact negatively on the patients' social functions and quality of life. Studies have shown that i.p injection of lipopolysaccharide (LPS) induces depressive-like behavior in rodents via induction of oxidative stress and neuroinflammation. Methyl jasmonate (MJ), an isolated compound from jasmine plant has gained reputation in aromatherapy for treatment of depression, nervousness and memory deficits. This study was designed to evaluate the effects of MJ on LPS-induced depressive-like behavior in mice. Mice were given MJ (5–20 mg/kg), imipramine (10 mg/kg) or vehicle (10 mL/kg) intraperitoneally for 7 consecutive days. On day 7, treatment was carried out 30 min prior to i.p injection of LPS (830 µg/kg). Twenty four hours after LPS administration, tail suspension, forced swim and sucrose preference tests were carried out. Thereafter, serum corticosterone levels were determined using ELISA. The levels of malondialdehyde (MDA), glutathione (GSH) and tumor necrosis factor-alpha (TNF-α) were determined in brain tissue homogenates. LPS significantly increased immobility time in the tail suspension and forced swim tests when compared with vehicle ($p < 0.05$), which indicates depressive-like syndromes. However, the increased immobility time was significantly reduced by MJ (5–20 mg/kg) when compared with LPS-treated group. LPS administration also altered the levels of MDA, GSH, corticosterone and TNF alpha in mice, which was significantly reversed by MJ. These findings suggest that attenuation of LPS-induced depressive-like behavior by MJ may be related to suppression of oxidative stress and release of TNF alpha.

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1. Introduction

Depression is a common psychiatric disorder, affecting the quality of life and overall productivity of the sufferers (Ferrari et al., 2013). Depression is an affective disorder characterized by change in mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep, appetite, low energy, psychomotor retardation and melancholia. Major depression is a severe health condition associated with high disability and it has a life time prevalence of about 10–15% (Kessing, 2012; Ferrari et al., 2013). The course of the disease is recurrent and most patients who recover from major depressive episodes still become depressed afterwards (Kessing, 2012; Gorwood et al., 2014). Moreover, repeated episodes of depression have been shown to cause atrophy of the

hippocampus thereby increasing the risk of dementia and also contribute to treatment failures (Kessing, 2012; Gorwood et al., 2014). Major depression has been reported to be a major economic burden beyond the direct costs of its treatment. The indirect and intangible costs, which include decreased productivity, morbidity and increased mortality, are known to account for about 70–80% of the total cost (Khoo et al., 2015). Current available antidepressant drugs have certain drawbacks such as limited spectrum of activity, slow onset of action, serious adverse effects and poor compliance (Lépine and Briley, 2011; Gautam et al., 2013; Kumari et al., 2016). Thus, the need to search for new drugs as alternative treatments for severe depression still persist (Gautam et al., 2013; Kumari et al., 2016).

There are increasing evidences that support the notion that depression is closely connected with inflammation in the brain (Dantzer et al., 2008; Capuron and Dantzer, 2003). Moreover, prevalence of depression has been reported to be higher in patients with chronic infections, cancers and rheumatoid arthritis (all of which have a common identity of chronic inflammation as the

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underlying factor) than in the normal population (Evans et al., 2005; Capuron and Dantzer, 2003; O'Connor et al., 2009). Moreover, proinflammatory cytokines including IL-6 and IL-1 β were elevated in the plasma or cerebrospinal fluid of depressed patients (O'Connor et al., 2009; Capuron and Dantzer, 2003) and these heightened levels of cytokines were associated with the severity of the disease (Yirmiya, 1996; O'Connor et al., 2009). Thus, the administration of the cytokine inducer lipopolysaccharide (LPS) is often used to produce depressive-like behavior, as measured by increased immobility in the forced-swim test (FST) and tail suspension test (TST), decreased consumption of a sweetened solution and a suppression of sexual behavior in laboratory animals, which can be attenuated by chronic antidepressant drugs (Yirmiya, 1996; O'Connor et al., 2009). Indeed, several studies have shown that systemic administration of LPS, a non-infectious component of a gram-negative bacterial cell produced behavioural changes that closely resemble depressive symptoms in humans (Yirmiya, 1996; De La Garza, 2005; Ge et al., 2015; Liu et al., 2016). Specially, LPS has been shown to cause behavioural and biochemical changes through induction of oxidative stress and neuroinflammation (De La Garza, 2005; Fan et al., 2014; Ge et al., 2015; Leonard and Maes, 2012; Miller et al., 2009; Qin et al., 2007). Thus, compounds with potent antioxidant and anti-inflammatory activities are being sought as alternatives for treatment of depression (Gautam et al., 2013).

Methyl Jasmonate (MJ) is a plant stress hormone that was first isolated from the essential oil of *Jasmonium grandiflorum* (Demole et al., 1962). It is secreted by plants in response to external stress and its level is known to increase when plants suffer wounds or infections (Cesari et al., 2014). The potential benefits of Jasmine flower for depression, nervousness, tension and memory deficits in aromatherapy have been reported in literature (Kuroda et al., 2005). Previous studies from our laboratory have shown that MJ possessed antinociceptive, anti-amnesic and adaptogenic properties in experimental models (Umukoro and Olugbemide, 2011; Eduviere et al., 2015; Umukoro et al., 2016). In addition, preliminary studies have also revealed that MJ exhibited antidepressant activity in naïve mice subjected to tail suspension and forced swim tests (Umukoro et al., 2011). However, this present study was designed to evaluate in details, its effects on LPS-induced depressive-like behaviors in mice and the likely mechanism(s) involved in its action.

2. Materials and methods

2.1. Experimental animals

Male Swiss mice (22–25 g) used in the study were obtained from the Central Animal House, University of Ibadan and were housed in plastic cages at room temperature with 12:12 h light–dark cycle. They were fed with rodent pellets and water *ad libitum*. The animals were allowed to acclimatize for few days before use in all experiments. The experimental procedures were approved by the University of Ibadan Animal Care and Use Research Ethics Committee (UIACUREC/App/2016/023).

2.2. Drugs and chemicals

Methyl jasmonate (5, 10, 20 mg/kg), imipramine (10 mg/kg) and lipopolysaccharide (830 μ g/kg) used in the study were obtained from Sigma, Germany. MJ was dissolved in 95% ethanol and further diluted with distilled water as previously described (Umukoro et al., 2011). Imipramine and LPS were dissolved in distilled water immediately before use. The doses of 5, 10 and 20 mg/kg of MJ used in this study were selected based on the results obtained from

previous studies (Umukoro et al., 2011). The dose of LPS (830 μ g/kg) and the time point (24 h) for behavioural tests after LPS administration were chosen based on previous investigations (O'Connor et al., 2009).

2.3. Experimental procedures

Mice were randomly divided into 6 treatment groups ($n = 6$). Mice in group 1 were given vehicle (1% ethanol, 10 mL/kg), groups 2–4 received MJ (5, 10 and 20 mg/kg) whereas group 5 were pre-treated with imipramine (10 mg/kg) daily for 7 days prior to i.p injection of LPS (830 μ g/kg). Mice in group 6 were also given vehicle but were not injected with LPS. All treatments were administered intraperitoneally. The behavioural studies were carried out 24 h after LPS administration and blood samples were collected afterwards for estimation of serum corticosterone levels. The animals were then sacrificed for various biochemical studies.

2.4. Behavioural studies

2.4.1. Sucrose preference test

Sucrose preference test was carried out 24 h after LPS treatment as previously described (Gronli et al., 2005). Briefly, 72 h before the test, mice were trained to adapt to 1% sucrose solution (w/v). Two bottles of 1% sucrose solution were initially placed in each cage and 24 h later, 1% sucrose in one of the bottles was replaced with water for another 24 h. After adaptation, mice were deprived of water and food for 12 h, followed by the sucrose preference test, in which mice were allowed free access to the two bottles containing 100 mL of 1% sucrose and 100 mL of water, respectively.

Afterwards, the volumes of sucrose solution and water consumed were recorded. Sucrose preference was calculated using the following formula:

$$\frac{\text{Sucrose consumption} \times 100}{\text{Sucrose consumption} + \text{water consumption}}$$

2.4.2. Tail suspension test and forced swim test

The tail suspension test was carried out according to the procedure described by Cryan et al. (2005). The animals were suspended individually on a retort stand, placed 50 cm above the floor with the help of an adhesive tape placed approximately 1 cm from the tip of the tail. The total duration of immobility were recorded during the last 4 min of the 6 min test. An animal was considered to be immobile when it did not show any movement of the body and hangs passively. In the forced swim test, mice were forced to swim individually in a glass jar (height: 20 cm, diameter: 10 cm) filled with water (depth: 15 cm) at a temperature of 25 ± 2 °C for 6 min. The duration of immobility (s) was recorded during the last 4 min of a 6 min observation period. A mouse was judged to be immobile when it remained floating in an upright position with the head above the water level.

2.4.3. Assessment of locomotor activity (SMA)

The SMA was measured using activity cage (Ugo Basile, Italy). The animals were placed individually in the center of the cage and the SMA, which was measured for a period of 5 min, was expressed as activity counts per 5 min.

2.5. Biochemical assays

2.5.1. Estimation of serum corticosterone levels

After behavioural testing, 1 mL of blood sample was obtained

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