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Original research article

Antidepressant-like activity of methyl jasmonate involves modulation of monoaminergic pathways in mice

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ABSTRACT

Purpose: The efficacy of current antidepressant drugs has been compromised by adverse effects, low remission and delay onset of action necessitating the search for alternative agents. Methyl jasmonate (MJ), a bioactive compound isolated from *Jasminum grandiflorum* has been shown to demonstrate antidepressant activity but its mechanism of action remains unknown. Thus, the role of monoaminergic systems in the antidepression-like activity of MJ was investigated in this study.

Materials and methods: Mice were given i.p. injection of MJ (5, 10 and 20 mg/kg), imipramine (10 mg/kg) and vehicle (10 mL/kg) 30 min before the forced swim test (FST) and tail suspension test (TST) were carried out. The involvement of monoaminergic systems in the anti-depressant-like effect of MJ (20 mg/kg) was evaluated using *p*-chlorophenylalanine (pCPA), metergoline, yohimbine, prazosin, sulpiride and haloperidol in the TST.

Results: MJ significantly decrease the duration of immobility in the FST and TST relative to control suggesting antidepressant-like property. However, pretreatment with yohimbine (1 mg/kg, i.p., an α_2-adrenergic receptor antagonist) or prazosin (62.5 μg/kg, i.p., an α_1-adrenoceptor antagonist) attenuated the antidepressant-like activity of MJ. Also, pCPA; an inhibitor of serotonin biosynthesis (100 mg/kg, i.p) or metergoline (4 mg/kg, i.p., 5-HT_2 receptor antagonist) reversed the anti-immobility effect of MJ. Sulpiride (50 mg/kg, i.p., a D_2 receptor antagonist) or haloperidol (0.2 mg/kg, i.p., a dopamine receptor antagonist) reversed the anti-immobility effect of MJ.

Conclusion: The results of this study suggest that serotonergic, noradrenergic and dopaminergic systems may play a role in the antidepressant-like activity of MJ.

1. Introduction

The involvement of monoamines such as noradrenaline, serotonin and dopamine in the pathophysiology of depression and the mechanism of action of antidepressant treatments has been recognized many years ago [1,2]. The findings that pharmacological agents that increase synaptic concentrations of monoamines improved the symptoms of depression was one of the major reasons for the adoption of the monoamine hypothesis of depression for over 30 years ago [3]. Despite emerging theories challenging this popular belief, the role of central serotonergic and noradrenergic systems in the mediation of depressive symptoms and basis for the current approaches to treatment of the disease still remains very strong [3,4]. However, currently available antidepressant drugs whose action centered primarily on the enhancement of monoaminergic neurotransmission are known to be associated with several debilitating adverse effects, delayed therapeutic responses, limited efficacy and ineffectiveness in certain patients in the population [4]. In addition, relapse, and recurrence; psychosocial and physical impairment; and a high suicide rate still occur despite availability of these drugs [5]. Thus, the need to continue to search for new agents with better efficacy and tolerability still persists.

Methyl jasmonate, MJ is a well known bioactive compound that was first isolated from the essential oil of *Jasminum grandiflorum*, a jasmine plant, noted for its sweet smelling flowers. Moreover, MJ is also found virtually in all species of plant kingdom including fruits

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and vegetables, which forms significant proportion of our diets [6]. MJ is well recognized as a hormone released by plants in response to various external stressors and its stress-protective effect has been linked to activation of intracellular defense mechanisms of the plant cells [7,8]. However, the therapeutic potentials of MJ as a potent agent for the treatment of a wide range of cancer have gained global recognition [6,9]. MJ has been shown in various studies to selectively kill cancer cells without affecting normal cells and detailed toxicological investigations also confirmed that it is very safe for human consumptions [6].

However, the role of MJ in neuropsychiatric disorders was envisaged based on the studies of Hossain et al. [10], which revealed that MJ enhanced GABA currents and demonstrated sedative effect when given through inhalation in rodents. Also, we have reported in our previous studies that MJ has anti-nociceptive [11], anti-aggressive [12], anti-amnesic [13] and adaptogenic or anti-stress [14] activities in validated animal models. Furthermore, the use of jasmine in aromatherapy for depression and jasmine tea to calm nerves [15] prompted us to investigate MJ for the first time for antidepressant activity in behavioural models predictive of clinical depression [16]. The findings from this previous study revealed that MJ exhibited antidepressant-like activity in mice [16] but its mechanism of action was yet to be elucidated. Thus, this present study was designed to investigate the possible role of monoaminergic systems in the anti-depression-like activity of MJ in mice (Scheme 1).

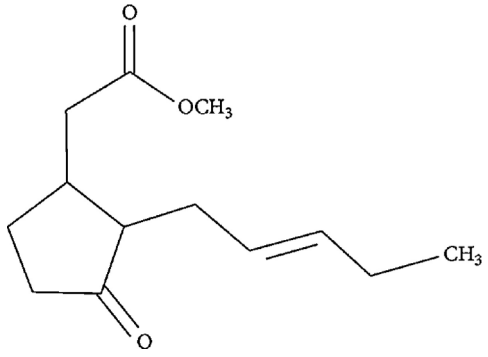
2. Materials and methods

2.1. Experimental animals

The male Swiss mice (20–25 g) used in the study were obtained from the Central Animal House of the University of Ibadan, Nigeria. The animals were kept at a temperature of about 26 °C with 12-h light:dark cycle and relative humidity of about 74%. They were fed with commercial rodent pellets and water ad libitum. The animals were allowed to acclimatize for at least one week before commencement of experiments. The experimental procedures were approved by the University of Ibadan Animal Care and Use Research Ethics Committee with approval number of UI-ACUREC/App/2015/030.

2.2. Drugs and chemicals

P-Chlorophenylalanine methyl ester (pCPA), sulpiride, prazosin, yohimbine, metergoline (all from Sigma Chemical Company, St. Louis, MO, USA) and methyl jasmonate (Sigma, Germany) were used in the study. Methyl jasmonate (MJ) was prepared according to the procedure previously described [11]. Briefly, 0.5 mL of MJ was dissolved in 4.5 mL of ethanol (95%) to obtain a stock solution, which was further diluted with distilled water to attain the concentration used in the study. The final concentration of ethanol in the solution used as vehicle in this study was 1% [11]. The other drugs were dissolved in distilled water immediately before use. The doses of methyl jasmonate used in the study were selected based on the results obtained from preliminary investigations. However, in order to elucidate the possible mechanisms by which MJ causes antidepressant-like action in the TST, the animals were treated with intraperitoneal injection of pCPA (100 mg/kg), metergoline (4 mg/kg), prazosin (62.5 μg/kg), yohimbine (1 mg/kg), sulpiride (50 mg/kg) and haloperidol (0.2 mg/kg). The doses of the drugs and the route of administration used in this study were chosen based on existing data in literature [17–19].



Scheme 1. Chemical structure of methyl jasmonate [6].

2.3. Drug treatment

All the drugs were administered via intraperitoneal (i.p) route. The animals were divided into five treatment groups (n = 6). Mice in group I, which served as control received vehicle (10 mL/kg), group 2 received imipramine (10 mg/kg), which served as the reference drug while groups 3–5 were given MJ (5, 10, and 20 mg/kg) 30 min before FST, TST and SMA were carried out.

2.4. Experimental procedures

2.4.1. Forced swim test (FST)

This test was carried out according to the method of Porsolt et al. [20]. The animals were divided into various treatment groups and administered with the various drugs as described earlier. Then, 30 min after treatment, each mouse was placed into a Plexiglas cylinder (25 cm height, diameter 10 cm containing water to a height of 10 cm at 25 °C) and observed for the duration of immobility (s) for a period of 6 min. A mouse was judged immobile if it floats in the water in an upright position and made only slight movements to prevent sinking. The total duration of immobility was recorded during the last 4 min of the 6 min test.

2.4.2. Tail suspension test (TST)

This test was carried out according to the method of Steru et al. [21]. A new set of animals were treated with the various drugs as described earlier. Thirty minutes after treatment, mice 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 was 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.

2.4.3. Test for spontaneous motor activity (SMA)

In order to rule out any unspecific locomotor effect of MJ, new set of mice were administered with the same regimen as in the FST or TST. The SMA was measured using activity cage (Ugo Basile, Italy). The animals were placed individually in the center of the cage 30 min after drug treatment and the SMA, which was measured for a period of 5 min, was expressed as activity counts/5 min.

2.4.4. Role of serotonergic system in antidepressant activity of MJ

In order to investigate the possible contribution of the serotonergic system to the antidepressant-like activity of MJ in the TST, the animals were pretreated with metergoline (4 mg/kg, ip., a 5-HT_2 receptor antagonist) 30 min prior to administration of the most effective dose of MJ (20 mg/kg, i.p.) and were tested in the TST 30 min later [19,22]. The possible role of the serotonergic