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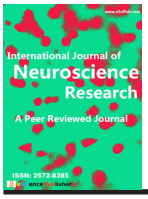

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Methyl jasmonate ameliorates memory deficits in mice exposed to passive avoidance paradigm

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ABSTRACT

Passive avoidance task is a rodent model of memory in which the animal learns to avoid an aversive stimulus precipitated by fear and it is always accompanied by inhibition of motor behavior. We have shown in our previous studies that methyl jasmonate (MJ), a bioactive compound isolated from *Jasminum grandiflorum* demonstrated memory enhancing effect in hippocampal-dependent memory tasks such as Y-maze and object recognition tests in mice. This present study was designed to investigate if MJ could ameliorate memory deficits associated majorly with the activation of the amygdala in response to an aversive stimulus in the passive avoidance paradigm. The present study also evaluated the effect of MJ on scopolamine (SC)- and lipopolysaccharide (LPS)-induced memory impairment in the passive avoidance paradigm. Mice were given intraperitoneal (i.p) injection of MJ (10-40 mg/kg), donepezil, DP (1 mg/kg) or vehicle daily for 7 days before testing for memory using passive avoidance step-down apparatus. In the interaction studies, the effects of SC (3 mg/kg, i.p.) or LPS (250 µg/kg, i.p.) given alone or with MJ (10, 20, 40 mg/kg) or DP (1 mg/kg) for 7 consecutive days were also evaluated. SC and LPS were injected 30 min after MJ or DP administration. The time it took (step-down latency) the mouse to step down from the elevated vibrating platform onto the grids (electrified stainless steel bars on the floor of the cage), which indicates memory function was recorded. Our findings revealed

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that MJ (10-40 mg/kg, i.p.) ameliorated memory deficits induced by electric shock in the passive avoidance test. MJ (10-40 mg/kg, i.p.) also attenuated memory impairment induced by SC (3 mg/kg) or LPS (250 µg/kg) in mice subjected to the shock in the passive avoidance task. Taken together, this study provides additional behavioral data, which further supports the potential usefulness of MJ in conditions associated with memory decline.

Keywords: Methyl jasmonate, memory deficit, passive avoidance, lipopolysaccharide, scopolamine

Introduction

Memory impairment results in the inability of the individuals to retain and recall learned information and knowledge of past events [1]. Several behavioral animal models such as Morris water maze, Y-maze, Barnes maze and object recognition are routinely used to assess novel compounds with memory enhancing effects in rodents [2-3]. However, these models unlike passive avoidance task do not employ aversive stimuli associated with fear as a condition of learning and memory acquisition [4-5]. Also, the brain fear center, amygdala is known to play a prominent role in the response of animals in the passive avoidance task even though the hippocampus is also involved in memory and learning in this behavioral model of cognition [6-8]. In the passive avoidance task, the animal learns to suppress a motor response to avoid exposure to the test area associated with or predictive of the aversive event, such as stepping down from the elevated platform onto the electric grid or a dark compartment of the passive avoidance apparatus that is usually preferred over the brightly illuminated compartment [5,9]. Thus, it is a fear conditioning emotional memory, which involves a recall of adverse experiences that provoke the animal to inhibit its behavior in order to avoid the unpleasant situations like the shock [6-9]. The passive avoidance test is very unique as a model of studying the interaction between punishment or aversive conditions and memory acquisition, which is quite crucial for the survival of the organisms (5-10). Thus, this study was carried out to further evaluate the memory promoting effects of methyl jasmonate (MJ) and its ability to reverse SC- and LPS-induced cognitive dysfunctions in mice exposed to aversive stimulus in the passive avoidance task. It is worthy to note that SC and LPS are commonly used to induce memory deficits in experimental animals and for the detection of novel compounds with anti-amnesic effects [11-13]. Memory impairment caused by SC is known to be related to antagonism of central cholinergic system whereas neuroinflammation has been implicated in the amnesic effect of LPS (11-13).

Methyl jasmonate (MJ) is an anti-stress hormone release by plants in response to abiotic and biotic stressors, but was however; first isolated from the flower of *Jasminum grandiflorum*, a beautiful ornamental and medicinal plant found in most tropical regions of the world [14-16]. It is interesting to note that MJ is very safe for human consumption, as it is present in most of the food we consumed as fruits and vegetables (16). It is also consumed as tea and used traditionally to relieve stress and tension; for treatment of depression and memory deteriorations [17]. Several studies have highlighted its health benefits against cancer, depression, amnesia and other neuropsychiatric disorders (14, 16, 18-21). Although we have reported in our previous studies that MJ improves memory and attenuated scopolamine or lipopolysaccharide-induced amnesia in object recognition and Y maze tests in mice [20-21], its effect on memory acquisition and consolidation in response to an aversive stimulus in passive avoidance task is yet to be investigated. Thus, this behavioral study was done to test for the memory promoting effect of MJ and its ability to reverse SC- and LPS-induced cognitive dysfunctions in mice exposed to aversive stimulus in the passive avoidance task.

2. Materials and methods

2.1. Laboratory animals

Adult albino Swiss mice weighing 22–25 g used in the study were obtained from the Central Animal House, University of Ibadan and were kept in plastic cages at room temperature with 12:12 h light–dark cycle. They were fed with

balanced rodent pellet diet and water *ad libitum*. Animals were acclimatized 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 (UI-ACUREC/App/2015/030) and performed in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals.

2.2. Drugs and chemicals

Methyl jasmonate (Sigma, Germany), donepezil (Pfizer, USA), scopolamine (BDH Chemicals Ltd., England) and lipopolysaccharide (Sigma, Germany) were used in the study.

2.3. Preparation of *methyl jasmonate*

The procedure for preparation of MJ and doses chosen for the study were based on the information previously reported by Eduviere et al., [21].

Experimental procedures

Passive Avoidance step-down paradigm

The effect of MJ on retention and retrieval of memory was assessed utilizing the passive avoidance step-down apparatus as previously described [22]. The step-down apparatus consists of a 28(w) x 23(d) x 26(h) cm perplex box with an electrified cage floor (40, 0.2cm stainless steel bars spaced 0.5cm apart) and an elevated vibrating platform (7cm). The animals were randomly distributed into treatment groups (n = 6) and were given MJ (10, 20, 40 mg/kg), DP (1 mg/kg) or vehicle (10 mL/kg) for 7 consecutive days. In the interaction studies, the effects of SC (3 mg/kg, i.p.) or LPS (250 µg/kg, i.p.) given alone or with MJ (10, 20, 40 mg/kg) or DP (1 mg/kg) for 7 consecutive days were also assessed. SC and LPS were injected 30 min after MJ or DP administration. Then, mice were placed individually on the elevated platform and, when the animal steps off the platform, a shock was induced. In this model, the one-trial step-down inhibitory avoidance was employed; which comprised of training and test sessions. In the training session; which was done on day 7, mice were placed individually on the elevated platform. Each animal received a scrambled foot shock of 0.5 mA for 5 s immediately it stepped down with its four paws on the grid. Thereafter, the animal was removed from the apparatus. In the test session, which was conducted 24 h after the training session; the mouse was also placed on the elevated platform but did not receive foot shock. The time it took (step-down latency) the mouse to step down from the elevated vibrating platform onto the grids (electrified stainless steel bars on the floor of the cage), which indicates memory was measured.

2.5. Statistical analysis

The data were analyzed using Graph Pad Prism software version 4.0 and expressed as mean ± S.E.M. Statistical analysis was done using one-way ANOVA, followed by Newman–Keuls post-hoc test. P values less than 0.05 were considered statistically significant.

3. Results

MJ increases step-down latency in passive avoidance task

The effect of MJ given daily for 7 days on memory function as measured by passive avoidance test is shown in Figure 1. MJ (10-40 mg/kg, i.p.) produced a significant ($p < 0.05$) increase in the latency to step-down from the vibrating elevated platform in comparison with vehicle, which suggest anti-amnesic activity (Fig. 1). The reference drug, donepezil (1 mg/kg, i.p.) also demonstrated anti-amnesic effect in this model (Fig 1).

Methyl jasmonate attenuates memory deficits induced by scopolamine in passive avoidance test

The effect of pretreatment of mice with MJ on SC-induced amnesia in passive avoidance task is shown in Figure 2. Intraperitoneal injection of SC (3 mg/kg, i.p) once daily for 7 consecutive days produced significant ($p < 0.05$) decrease in step-down behaviors of mice when compared with vehicle suggesting amnesic effect or memory impairment. However, as shown in Figure 2, MJ (10-40 mg/kg, i.p) or DP (1 mg/kg, i.p) administered daily for 7 days significantly ($p < 0.05$) attenuated SC (3 mg/kg)-induced memory deficits in mice.

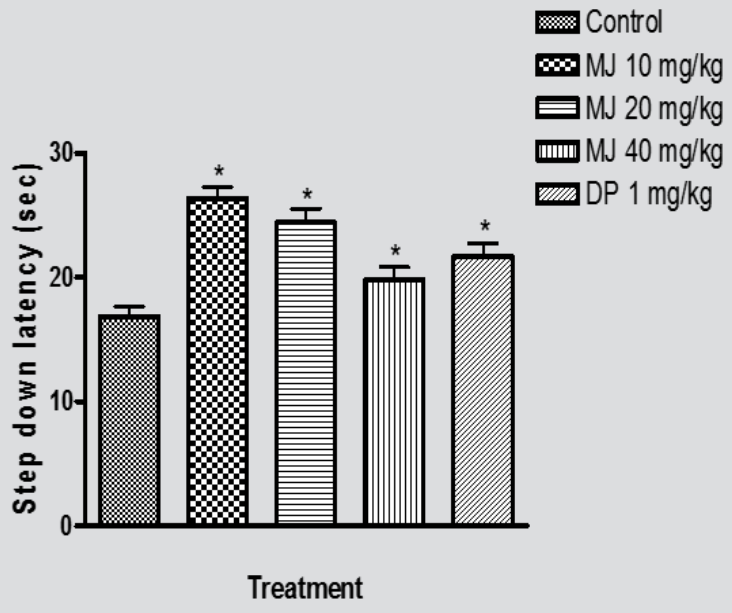

Fig. 1. Effect of methyl jasmonate on memory performance in passive avoidance step-down test in mice. Values represent the mean ± S.E.M. for 6 animals per group. *p < 0.05 compared with control group (ANOVA followed by Newman–Keuls test).

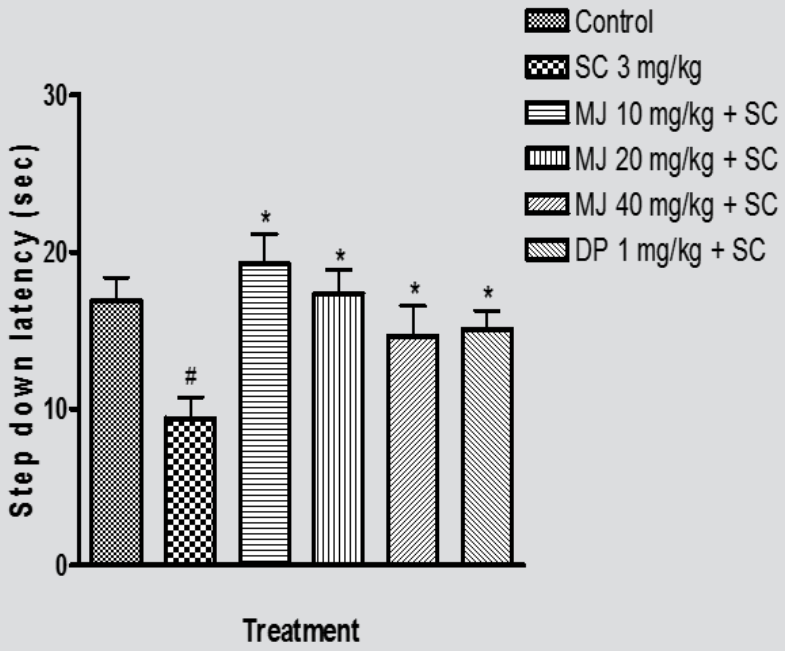

Fig. 2. Effect of methyl jasmonate on step-down latency in scopolamine- treated mice. Values represent the mean ± S.E.M. for 6 animals per group. #p < 0.05 compared with control group (ANOVA followed by Newman–Keuls post hoc test). *p < 0.05 compared with scopolamine group (ANOVA followed by Newman–Keuls post hoc test).

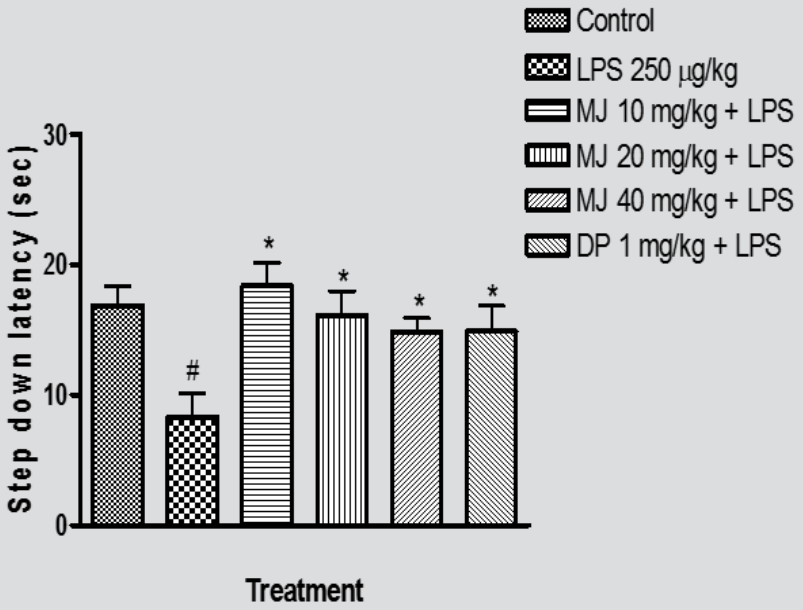

Fig. 3. Effect of methyl jasmonate on step-down latency in lipopolysaccharide-treated mice. Values represent the mean ± S.E.M. for 6 animals per group. $^{\#}p < 0.05$ compared with control group (ANOVA followed by Newman–Keuls post hoc test). $^{*}p < 0.05$ compared with scopolamine group (ANOVA followed by Newman–Keuls post hoc test).

Effect of methyl jasmonate on lipolysaccharide- induced memory impairment

As shown in Figure 3, intraperitoneal injection of LPS (250 μg/kg) for 7 consecutive days decreased the latency to step-down from the vibrating platform onto the electric grid of the passive avoidance apparatus relative to the vehicle indicating memory impairment. However, MJ reversed the memory deficits ($p < 0.05$) induced by LPS (250 μg/kg) in mice in a similar manner to DP (1 mg/kg, i.p) in the passive avoidance task (Fig. 3).

Discussion

The effect of MJ on retention and retrieval of memory was assessed in this study using passive avoidance test. This model is employed in screening the effect of compounds on implicit memory and it involves learning ability to avoid an aversive stimulus. Since, this is a form of punishment to the natural exploratory drive of a rodent; the animal tends to avoid the area containing the aversive stimulus [5, 22]. This involves both explicit, associative component and operant-like conditioning, which is being considered as a type of implicit memory [22]. Our results further showed that MJ has anti-amnesic effect as evidenced by a significant prolongation in the step-down latency in the passive avoidance task. Moreover, cognitive impairment induced by SC or LPS as shown by decrease step-down latency was also attenuated by MJ. These findings further support our previous studies, which showed that MJ has memory enhancing effect in Y-maze and object recognition animal model of cognition (20-21).

Several behavioral animal models of cognition exist in literature [2-3] however the passive avoidance task is very unique, as it employed aversive stimuli as a conditioned process of learning and memory acquisition (4-8). Also, the brain fear center, amygdala has been reported to play a prominent role in the response of animals in the passive avoidance task whereas the hippocampus is majorly involved in memory and learning in other animal models of cognition [7-8]. In the passive avoidance task, the animal learns to suppress a motor response to avoid exposure to the test area associated with or predictive of the aversive event, such as stepping down from the platform on the electric grid or a dark compartment of the passive avoidance apparatus that is normally preferred over the brightly illuminated compartment [5,9]. Thus, it

is a fear conditioning emotional memory, which involves a recall of adverse experiences that provoke the animal to inhibit its behavior in order to avoid the unpleasant situations like the shock. The passive avoidance apparatus is very unique as a model of studying the interaction between punishment or aversive conditions and memory acquisition, which is quite crucial for the survival of organism [6-10]. Thus, the findings that MJ prolonged the step-down latency indicate that it may help the organisms to recall the aversive experience associated with aversive situations that typify good memory.

Scopolamine and LPS are commonly used to induce memory deficits in experimental animals and for the detection of compounds with anti-amnesic effects [11-13]. Memory impairment caused by SC is known to be related to inhibition of central cholinergic system whereas neuroinflammation has been implicated in the amnesic effect of LPS (11-13). It has been reported that central cholinergic dysfunction and a deregulated neuroinflammatory processes are closely connected with the pathophysiology of AD [23-26]. In addition, the memory deficits produced by SC and LPS have been reported be related to changes in neuronal functions that are similar to AD pathology [23-28]. Although this investigation provides additional behavioral data that supported the memory enhancing effect of MJ, further studies are ongoing in our laboratory to elucidate the mechanism (s) underlying its anti-amnesic effect in the passive avoidance task.

In conclusion, the present study showed that methyl jasmonate exhibited memory promoting effect and attenuated cognitive dysfunctions produced by SC or LPS in passive avoidance model, which further confirmed its potential usefulness in conditions associated with cognitive deteriorations.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgments

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