Pharmacology, Biochemistry and Behavior 98 (2011) 8–11

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Antidepressant activity of methyl jasmonate, a plant stress hormone in mice

Solomon Umukoro [a,*], Alabi O. Akinyinka [b], Aderemi C. Aladeokin [a]

[a] Department of Pharmacology and Therapeutics, University of Ibadan, Ibadan, Nigeria
[b] Health Services, Olabisi Onabanjo University, Ago Iwoye, Nigeria

ARTICLE INFO

Article history:
Received 28 July 2010
Received in revised form 30 November 2010
Accepted 2 December 2010
Available online 8 December 2010

Keywords:
Methyl jasmonate
Forced swim test
Tail suspension test
Yohimbine lethality test
Antidepressant

ABSTRACT

Methyl jasmonate (MJ) is a hormone released by plants in response to external stress, injury or pathogenic invasions. This present investigation evaluated the antidepressant effect of intraperitoneal doses of MJ in mice. Mice were given MJ in the doses of 10, 25 and 50 mg/kg daily for 7 days and then subjected to forced swim test (FST), tail suspension test (TST) and yohimbine lethality test (YLT). The results showed that MJ produced a significant decrease in the period of immobility in the FST and TST, indicating antidepressant activity. MJ potentiated the toxic effect of yohimbine in the YLT, which further suggests antidepressant property and also indicates facilitatory effect on both serotonergic and noradrenergic systems respectively. However, MJ did not significantly alter the spontaneous motor activity of the animals, which indicates a lack of central nervous system stimulant effect. Taken together, these findings suggest that MJ has antidepressant activity and the mechanisms underlying this effect may involve serotonergic and noradrenergic systems.

1. Introduction

Depression is a common psychiatric disorder, often refractive to drug treatment, affecting quality of life and overall productivity (Schechter et al., 2005). The lifetime prevalence of depression is as high as 20% in the general population worldwide with a female to male ratio of about 5:2 (Kendler et al., 2001). Typically, the course of the disease is recurrent and most patients who recover from major depressive episodes still become depressed afterwards (Lavori et al., 1994). Although, several classes of antidepressants are currently being used, due to clinical limitations and adverse effects, there is critical interest in development of efficient and safe drugs for treatment of depression (Tran et al., 2003).

During the last decade, there is a growing interest in the therapeutic effects of natural products on mental disorders. In particular, the antidepressant effects of many plant preparations have been investigated, this has led to the discovery of St. John's wort, as an effective therapeutic agent for the treatment of depression (Deltito and Beyer, 1998; Tesch, 2003; Chatterjee et al., 1998). MJ is a plant stress hormone that was first isolated from the essential oil of *Jasminum grandiflorum*. MJ is secreted by plants in response to external stress and its level rises rapidly when plants suffer injury and pathogenic invasions (Fingrut et al., 2005). Previous studies showed that MJ has anticancer and anti-parasitic activities (Fingrut et al., 2005). It was shown to be toxic towards cancer cells without affecting normal cells (Fingrut and Flescher, 2002; Fingrut et al., 2005). While the anticancer activity of MJ is well documented in literature, there are no pharmacological data that indicated the role of this plant stress hormone in depression especially as stress and depression share common neuroanatomical and neurochemical substrates and circuits. Based on this premise, the present study investigated the antidepressant activity of MJ in mice.

2. Materials and methods

2.1. Experimental animals

Albino Swiss mice (18–25 g) of either sex were obtained from the Central Animal House, University of Ibadan. The animals were housed in plastic cages at room temperature with 12:12 h light–dark cycle. The animals had free access to commercial food pellets and water *ad libitum*. The animals were acclimatized for at least one week before they were used for all experiments. The experimental procedures were in compliance with National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985). The male and female animals were equally distributed in all the experiments.

2.2. Drugs

Imipramine (IM) hydrochloride (Sigma-Aldrich, St. Louis, USA), yohimbine (Sigma, USA) and methyl jasmonate (Sigma-Aldrich Chemie GmbH, Steinheim, Germany) were used in the study. Methyl jasmonate was dissolved in ethanol and this solution was further diluted with distilled water. The final concentration of ethanol in the

* Corresponding author. Tel.: +234 8130897439.
E-mail address: umusolo@yahoo.com (S. Umukoro).

0091-3057/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2010.12.001

solution used for the study did not exceed 1%. The other drugs were dissolved in distilled water immediately before use.

2.3. Drug treatment

The animals were pretreated intraperitoneally (i.p.) with MJ (10–50 mg/kg), IM (25 mg/kg) or vehicle (10 ml/kg of 1.0% ethanol) daily for 7 days. The doses of 10, 25 and 50 mg/kg of MJ used in the study were selected based on the results obtained from preliminary investigations. All the experimental procedures were started on day 7, 30 min after the drug administration.

2.4. Experimental procedures

2.4.1. Forced swim test (FST)

The FST was carried out according to the method of Porsolt et al. (1978). Mice (6/group) were forced to swim individually in a glass jar (height: 20 cm, diameter: 10 cm) filled with water (depth: 15 cm). The temperature of water was maintained at 25 ± 2 °C. The duration of immobility 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 and exhibited only small movements to keep its head above the water level.

2.4.2. Tail suspension test (TST)

The TST was carried out according to the method previously described (Steru et al., 1985; Cryan et al., 2005; Zomkowski et al., 2006). Mice (6/group) were individually suspended by the tail to a cord of about 50 cm in length stretched between two metal tripods at a height of 70 cm. After the initial 2 min period of vigorous motor activity, the mice became still and the immobility time was measured with a stopwatch, for a total duration of 4 min. Mice were considered immobile when they hung passively and completely motionless (Steru et al., 1985).

2.4.3. Yohimbine lethality test

The antidepressant effect of MJ was further evaluated utilizing the potentiation of yohimbine-induced lethality test in mice, as previously described (Malick, 1983). Mice (10/group) received i.p dose of 35 mg/kg of yohimbine and were immediately placed in cages. The numbers of death in each group were recorded 18 h after yohimbine administration.

2.4.4. Open field test

Mice (6/group) were placed individually in an open field (35 cm × 30 cm × 22 cm) and allowed to habituate to the new environment for 2 min. Subsequently, the time spent (s) in ambulation was counted manually for a period of 10 min as previously described (Swiergiel and Dunn, 2007).

2.5. Statistical analysis

The data were expressed as mean ± S.E.M. The data were analyzed with Graph Pad Prism software version 4.03. Statistical analysis of data was done by One-way ANOVA, followed by Tukey post-hoc test. A level of $p<0.05$ was considered as statistically significant.

3. Results

3.1. Forced swim test

Table 1 shows the effect of MJ on the duration of immobility time in the FST. One-way ANOVA revealed that there were significant differences between treatment groups [F (4, 24) = 40.28, $P<0.05$)]. Post-hoc analysis showed that the MJ (10, 25 and 50 mg/kg) and IM treated groups were significantly different ($p<0.05$) from the vehicle treated group. MJ significantly decreased the duration of immobility time, which indicates antidepressant effect. The effect of MJ was comparable to that of the reference drug, IM.

Table 1
Effect of methyl jasmonate on the duration of immobility in the forced swim test in mice.

Treatment	Dose (mg/kg)	Duration of immobility (s)
Control	–	158.50 ± 3.09
Methyl jasmonate	10	103.67 ± 7.69*
Methyl jasmonate	25	70.17 ± 5.71*
Methyl jasmonate	50	80.66 ± 6.30*
Imipramine	25	66.01 ± 6.18*

Each value represents the mean ± S.E.M ($n=6$ per group). *$p<0.05$ compared to the vehicle control group (ANOVA followed by Tukey post-hoc test).

3.2. Tail suspension test

The effects of MJ (10–50 mg/kg, i.p) on the duration of immobility in the TST are indicated in Table 2. One-way ANOVA reveals that there were significant differences between treatment groups [F (4, 24) = 124.10, $P<0.05$)]. Post-hoc analysis showed that the MJ (10, 25 and 50 mg/kg) and IM treated groups were significantly different ($p<0.05$) from the vehicle treated group. MJ significantly ($p<0.05$) shortened the duration of immobility in the tail suspension test, which indicates antidepressant effect. The effect produced by MJ at an i.p dose of 25 mg/kg, is comparable to that produced by IM (25 mg/kg, i.p).

3.3. Yohimbine lethality test

The effect of MJ (10, 25 and 50 mg/kg, i.p.) on yohimbine-induced lethality are depicted in Fig. 1. Post-hoc analysis showed that MJ (25–50 mg/kg, i.p.) administered 30 min before i.p injection of yohimbine (35 mg/kg) significantly ($p<0.5$) potentiated the lethal effect of yohimbine and the effect was comparable to that of IM. However, at a dose of 10 mg/kg, MJ did not significantly ($p>0.05$) potentiate the toxic effect of yohimbine in mice (Fig. 1). Although, MJ, at i.p. doses of 25 and 50 mg/kg, significantly potentiated the lethal effect of yohimbine, it did not produce any toxic symptoms or death in mice when administered alone.

3.4. Open field test in mice

Table 3 indicates the effects of MJ on motor activity of the animals in an open field.

One-way ANOVA indicated that there were no significant differences in motor activity of the animals when treated with daily doses of MJ (10–50 mg/kg, i.p) for 7 days [F(4, 24) = 0.1640, $P>0.05$] as compared to vehicle. As shown in Table 3, MJ did not significantly ($p>0.05$) alter the time of ambulation of the animals in comparison to the control group.

Table 2
Effect of methyl jasmonate on the duration of immobility in the tail suspension test in mice.

Treatment	Dose (mg/kg)	Duration of immobility (s)
Control	–	91.33 ± 3.46
Methyl jasmonate	10	45.67 ± 4.39*
Methyl jasmonate	25	19.50 ± 1.41*
Methyl jasmonate	50	22.30 ± 1.84*
Imipramine	25	23.05 ± 2.03*

Data are expressed as mean ± SEM ($n=6$/group).
* $p<0.05$ compared to the vehicle control group (ANOVA followed by Tukey post-hoc test).

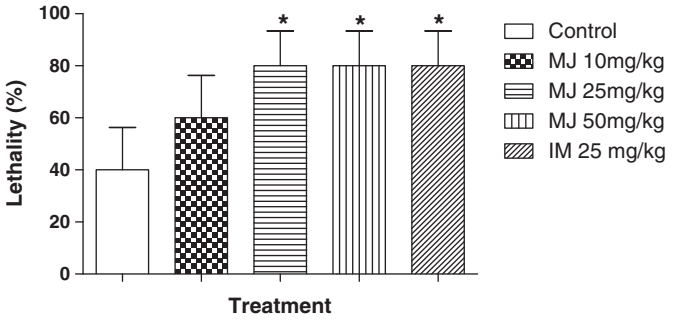

Fig. 1. Effect of methyl jasmonate on yohimbine-induced lethality in mice. Each column represents the mean ± S.E.M ($n = 10$/group).

4. Discussion

The present study shows that MJ significantly reduced immobility period in the forced swim and tail suspension tests in mice, which suggests antidepressant effect. Immobility is believed to reflect either a failure to persist in escape directed behavior after persistent stress or the development of passive behavior that disengages the animal from active forms of coping with stressful events (Kirby and Lucki, 1997). The FST and TST are valid behavioral models used frequently to evaluate the potential efficacy of prospective antidepressant drugs in rats or mice (Porsolt et al., 1978; Steru et al., 1985). Nordrenaline and serotonin have been identified as the neurochemical substrates involved in the mediation of behavioral response in the FST and TST (Roche et al., 2003; Kirby and Lucki, 1997). The behavioral immobility is selectively decreased by a variety of antidepressant drugs (Adell et al., 2005; Porsolt et al., 1978; Borsini and Meli, 1988). The yohimbine lethality test (YLT) was further used to validate and to explore the possible mechanism underlying the antidepressant activity of MJ in mice. YLT is a validated model for screening compounds with antidepressant property (Malick, 1983). Antidepressant drugs are known to potentiate the lethal effects of yohimbine through enhancement of both serotonergic and noradrenergic transmissions (Malick, 1983). The ability of MJ to potentiate the toxic effect of yohimbine therefore indicates antidepressant activity.

The pathogenesis of depression has been shown to be due to a deficiency of monoaminergic transmitters especially norepinephrine and serotonin in the brain (Schildkraut, 1965). Studies implicating serotonin and noradrenaline in the pathogenesis of depression are well reported in literature both in preclinical and clinical investigations (Blier, 2003; Anguelova et al., 2003). Reduction in brain serotonin and noradrenaline have been reported to be one of the most important etiological factors for genesis of depression and antidepressants increase extracellular availability of these transmitter amines in the brain (Anguelova et al., 2003; Drevets, 2001; Schildkraut, 1965; Adell et al., 2005). Studies have shown also that the anti-immobility exhibited by antidepressants in the FST and TST is mediated through facilitation of both serotonergic and noradrenergic neurotransmissions (Hajos et al., 2000; Kirby and Lucki, 1997). Although, the specific mechanism of action of MJ needs to be explored before coming to any conclusions on its mechanism of action, preliminary investigations suggest that its antidepressant effect may involve serotonergic and noradrenergic mechanisms. This suggestion is supported by the finding that MJ enhanced the lethal effect of yohimbine in mice. Previous studies have shown that yohimbine interferes both with noradrenaline (NA) and serotonin (5-HT) neurochemistry and further show the potential utility of the drug as a tool to test the involvement of serotonergic processes in endogenous depression (Papeschi et al., 1971; Söderpalm et al., 1971).

The major event involved in yohimbine toxicity is an overall increase in serotonergic and noradrenergic mechanisms (Malick, 1983). Yohimbine, an α_2-adrenergic receptors antagonist, stimulates sympathetic centers in the brain, leading to an increased sympathetic discharge both in the central and peripheral nervous systems (Goldberg and Robertson, 1983). The antagonism of α_2-adrenergic receptors promotes the release of noradrenaline from stores or nerves as a consequence of increased central sympathetic activity (Goldberg and Robertson, 1983). Furthermore, antagonism of α_2-adrenergic receptors also induces serotonin release, which further contributes to the overall toxicity caused by yohimbine (Siqueira et al., 1998; Quinton, 1963). Antidepressants are known to potentiate yohimbine-induced lethality by enabling the amines to reach the receptors in greater amounts, either by inhibiting their reuptake or by reducing their inactivation (Siqueira et al., 1998; Malick, 1983; Quinton, 1963). The ability of MJ to potentiate the lethal effect of yohimbine further suggests the involvement of serotonergic and noradrenergic mechanisms in its antidepressant activity. However, further study involving the use of microdialysis is required to precisely define the role of serotonin and noradrenaline in the antidepressant activity of MJ.

It is pertinent to note that although MJ potentiated the lethal effect of yohimbine, it did not cause any toxic symptoms when administered alone in mice. In another study, we reported that MJ administered intraperitoneally in doses ranging from 50 to 500 mg/kg was well tolerated by mice, as it did not produce toxic symptoms or death in the animals (Umukoro and Abimbola, 2010). This finding further support previous investigations, which show that MJ is safe, as it is not toxic to normal body cells (Fingrut and Flescher, 2002; Rotem et al., 2005; Cohen and Flescher, 2009).

It has been reported that psychomotor stimulant drugs mimic antidepressant-like behavioral outcome of rodents in forced swim tests (Porsolt et al., 1978; Sherman et al., 1982). Thus, the assessment of spontaneous locomotor activity is imperative as part of the routine procedures for detecting prospective antidepressant drugs (Porsolt et al., 1978). Antidepressants are known to reduce immobility at doses that do not change the motor behavior of rodents in open field tests (Kirby and Lucki, 1997). The open field test is commonly used to assess the locomotor activity and exploratory behavior of rats or mice (Keeney and Hogg, 1999). MJ did not significantly alter the spontaneous motor activity of the animals, which indicates a lack of psychomotor stimulant property.

In summary, the present study reveals that MJ has antidepressant activity and the mechanisms underlying this effect may involve facilitation of both serotonergic and noradrenergic neurotransmissions.

Table 3
Effect of methyl jasmonate on spontaneous motor activity in mice.

Treatment	Dose (mg/kg)	Ambulation time (s)
Control	–	60.50 ± 6.28
Methyl jasmonate	10	61.33 ± 2.73
Methyl jasmonate	25	62.00 ± 2.70
Methyl jasmonate	50	64.17 ± 5.55
Imipramine	25	59.10 ± 4.39

Data are expressed as mean ± SEM ($n = 6$/group). Test drugs did not significantly ($p > 0.05$) alter the ambulation time of the animals when compared with vehicle treatment (ANOVA followed by Tukey post-hoc test).

Acknowledgements

We thank Prof. O.G Ademowo, who kindly provided the methyl jasmonate for the study, and Mrs B. Arionla, for her technical assistance.

References

Adell A, Castro E, Celada P, Bortolozzi A, Pazos A, Artigas F. Strategies for producing faster acting antidepressants. Drug Discov Today 2005;10:578–85.
Anguelova M, Benkelfat C, Turecki G. A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behavior. Mol Psychiatry 2003;8:646–53.

Blier P. The pharmacology of putative early-onset antidepressant strategies. Eur Neuropsychopharmacol 2003;13:57–66.
Borsini F, Meli A. Is the forced swimming test a suitable model for revealing antidepressant activity? Psychopharmacology 1988;94:147–60.
Chatterjee SS, Bhattacharya K, Wonnemann M, Singer A, Müller WE. Hyperforin as a possible antidepressant component of Hypericum extract. Life Sci 1998;65: 2395–405.
Cohen S, Flescher E. Methyl jasmonate: a plant stress hormone as an anti-cancer drug. Phytochemistry 2009;70:1600–9.
Cryan JP, Mombereau C, Vassout A. The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. Neurosci Biobehav Rev 2005;29:571–625.
Deltito J, Beyer D. The scientific, quasi-scientific and popular literature on the use of St. John's Wort in the treatment of depression. J Affect Disord 1998;51:345–51.
Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive–emotional features of mood disorders. Curr Opin Neurobiol 2001;11:240–9.
Fingrut O, Flescher E. Plant stress hormones suppress the proliferation and induce apoptosis in human cancer cells. Leukemia 2002;16:608–16.
Fingrut O, Reischer D, Rotem R, Goldin N, Altboum I, Zan-Bar I, et al. Jasmonates induce nonapoptotic death in high-resistance mutant p53-expressing B-lymphoma cells. Br J Pharmacol 2005;146:800–8.
Goldberg MR, Robertson D. Yohimbine: a pharmacological probe for study of the α_2-adrenoceptor. Pharmacol Rev 1983;35:143–80.
Hajos KE, Mctavish SF, Sharp T. Effect of a selective 5-hydroxytryptamine reuptake inhibitor on brain extracellular noradrenaline: microdialysis studies using paroxetine. Eur J Pharmacol 2000;407:101–7.
Keeney AJ, Hogg S. Behavioural consequences of repeated social defeat in the mouse: preliminary evaluation of a potential animal model of depression. Behav Pharmacol 1999;10:753–64.
Kendler KS, Gardner CO, Neale MC, Prescott CA. Genetic risk factors for major depression in men and women: similar or different heritabilities and same or partly distinct genes? Psychol Med 2001;31:605–16.
Kirby LG, Lucki I. Interaction between the forced swimming test and fluoxetine treatment on extracellular 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in the Rat. J Pharmacol Exp Ther 1997;282:967–76.
Lavori PW, Keller MB, Scheftner W, Fawcett J, Mueller Tl. Recurrence after recovery in unipolar MDD. An observational follow-up study of clinical predictors and somatic treatment as a mediating factor. Int J Methods. Psychiatry Res 1994;4: 211–29.
Malick JB. Potentiation of yohimbine-induced lethality in mice: predictor of antidepressant potential. Drug Dev Res 1983;3:357–63.
Papeschi R, Sourkes TL, Youdim MBH. The effect of yohimbine on brain serotonin metabolism, motor behavior and body temperature of the rat. Eur J Pharmacol 1971;15:318–26.
Porsolt RD, Anton G, Deniel M, Jalfre M. Behavioral despair in rats: a new animal model sensitive to antidepressant treatments. Eur J Pharmacol 1978;47:379–91.
Quinton RM. The increase in the toxicity of yohimbine induced by imipramine and other drugs in mice. Br J Pharmacol Chemother 1963;21:51–66.
Roche M, Commons KG, Peoples A, Valentino RJ. Circuitry underlying regulation of the serotonergic system by swim stress. J Neurosci 2003;23:970–7.
Rotem R, Heyfets A, Fingrut O, Bickstein D, Shaklai M, Flescher E. Jasmonates: novel anticancer agents acting directly and selectively on human cancer cell mitochondria. Cancer Res 2005;65:1984–93.
Schechter LE, Ring RH, Beyer CE, Hughes ZA, Khawaja X, Malberg JE, et al. Innovative approaches for the development of antidepressant drugs: current and future strategies. NeuroRx 2005;2:590–611.
Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 1965;122:509–22.
Sherman AD, Sacquitne JL, Petty F. Specificity of the learned helplessness model of depression. Pharmacol Biochem Behav 1982;16:449–54.
Siqueira IR, Lara FS, Silva DR, Gaieski D, Nunes DS, Elisabetsky E. Psychopharmacological properties of *Ptychopetalum olacoides* Bentham (Olacacaeae). Pharm Biol 1998;36: 327–34.
Söderpalm A, Blomqvist O, Söderpalm B. The yohimbine-induced anticonflict effect in the rat. I: Involvement of noradrenergic, serotonergic and endozepinergic(?) mechanisms. Eur J Pharmacol 1971;15:318–26.
Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology 1985;85:367–70.
Swiergiel AH, Dunn AJ. Effects of interleukin-1beta and lipopolysaccharide on behavior of mice in the elevated plus-maze and open field tests. Pharmacol Biochem Behav 2007;86:651–9.
Tesch BJ. Herbs commonly used by women: an evidence-based review. Am J Obstet Gynecol 2003;188:S44–55.
Tran PV, Bymaster FP, McNamara RK, Potter WZ. Dual monoamine modulation for improved treatment of major depressive disorder. J Clin Psychopharmacol 2003;23:78–86.
Umukoro S., Abimbola S.O. Antinociceptive effects of methyl jasmonate in experimental animals. M.Sc Thesis. Department of Pharmacology and Therapeutics. University of Ibadan. 2010; 75 pp.
Zomkowski AD, Santos AR, Rodrigues AL. Putrescine produces antidepressant-like effects in the forced swimming test and in the tail suspension test in mice. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1419–25.