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ORIGINAL ARTICLE

Contribution of serotonergic and nitrergic pathways, as well as monoamine oxidase-a and Na^+, K^+-ATPase enzymes in antidepressant-like action of ((4-*tert*-butylcyclohexylidene) methyl) (4-methoxystyryl) sulfide (BMMS)

Renata L. de Oliveira[1] · Guilherme T. Voss[1] · Jaini J. Paltian[1] · Mikaela P. Pinz[1] · Marina Laura C. P. Torres[1] · Michele P. Moreira[2] · Marina C. Dilelio[3] · Claudio C. Silveira[3] · Ethel A. Wilhelm[1] · Cristiane Luchese[1]

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Abstract

The present study investigated a possible antidepressant-like effect of ((4-*tert*-butylcyclohexylidene)methyl) (4-methoxystyryl) sulfide (BMMS) by using the forced swimming test (FST) and the tail suspension test (TST) in Swiss mice. The contribution of serotoninergic, glutamatergic and nitrergic systems in the antidepressant-like activity of BMMS was evaluated. We also examined the involvement of monoamine oxidase (MAO)-A, MAO-B and Na^+, K^+-ATPase activities in prefrontal cortex of mice. BMMS, (0.1–10 mg/kg, intragastrically (i.g.)) and fluoxetine (32 mg/kg, i.g.) decreased the immobility time in the FST and TST. The anti-immobility effect of BMMS (10 mg/kg, i.g.) in the TST was prevented by the pretreatment of mice with WAY100635 (0.1 mg/kg, subcutaneously (s.c.), a 5-HT_{1A} receptor antagonist), ketanserin (5 mg/kg, intraperitoneal (i.p.), a 5-$HT_{2A/2C}$ receptor antagonist), and partially blocked by ondansetron (1 mg/kg, i.p., a 5-HT_3 receptor antagonist). The anti-immobility effect of BMMS (10 mg / kg, i.g.) was not avoided by pretreatment with MK-801 (0.01 mg/kg, s.c. a non-competitive N-methyl D-Aspartate (NMDA) receptor) in the TST. Pretreatment with L-arginine (500 mg/kg, i.p., a nitric oxide precursor) reversed partially the reduction in the immobility time elicited by BMMS (10 mg/kg, i.g.) in TST. BMMS altered Na^+,K^+-ATPase and MAO-A activities in prefrontal cortex of mice, but was not able to change the MAO-B activity. In conclusion, BMMS exerted an antidepressant-like effect in mice and serotonergic and nitrergic systems are involved in the antidepressant-like action of compound. BMMS modulated MAO-A and Na^+, K^+- ATPase activities in prefrontal cortex of mice.

Keywords Sulfur · Depression · Serotonin · Nitric oxide · Na^+ · K^+-ATPase · Monoamine oxidase

Introduction

Depression is a chronic multi-factorial and incapacitating psychiatric disorder, characterized by a triad of symptoms with low or depressed mood, anhedonia, and low energy or fatigue. Other emotional and physical symptoms are also often present, such as sleep and psychomotor disturbances, feelings of guilt, difficulty concentrating, low self-esteem, suicidal tendencies, as well as autonomic and gastrointestinal disturbances (McKenna et al. 2015). This disorder affects up to 16% of the population and has become the main cause of disability worldwide (Converge 2015). The World Health Organization (WHO) numbered depression as the fourth leading cause of disability worldwide, demonstrating the great impact of this disease on modern society (WHO 2010).

Depression is a heterogeneous disorder and a complex phenomenon, which has many subtypes and probably more than

✉ Ethel A. Wilhelm
ethelwilhelm@yahoo.com.br

✉ Cristiane Luchese
cristiane_luchese@yahoo.com.br

[1] Programa de Pós-graduação em Bioquímica e Bioprospecção, Laboratório de Pesquisa em Farmacologia Bioquímica (LaFarBio), Grupo de Pesquisa em Neurobiotecnologia (GPN), Centro de Ciências Químicas, Farmacêuticas e de Alimentos, Universidade Federal de Pelotas, Campus Capão do Leão, Pelotas, RS CEP 96010-900, Brazil

[2] Programa de Pós-Graduação em Nanociências, Centro de Ciências Tecnológicas, Universidade Franciscana, Santa Maria, RS CEP 97010-032, Brazil

[3] Departamento de Química, Universidade Federal de Santa Maria, Santa Maria, RS CEP 97105-900, Brazil

one etiology. The most accepted hypothesis to explain the depression pathophysiology is the monoaminergic, which postulates that there are abnormalities in the monoaminergic neurotransmitters, such as serotonin (5-HT), norepinephrine (NE) and/or dopamine (DA), that play important role in behavioral alterations (Menard et al. 2015; Finberg and Rabey 2016). Moreover, evidence also indicated that glutamatergic and nitrergic pathways are implicated in the pathogenesis of depressive disorders (Sanacora et al. 2008). In this way, the pathophysiological aspects of depressive disorders are not yet fully understood.

Nowadays there are several treatments and new drug regimen available for depressive disorders. However, these treatments have significant limitations, such as low response rates, treatment resistance, high incidence of relapse, and a time-lag of weeks to months for a response (Trivedi et al. 2006). In this context, there is a major unmet need for more efficacious and faster-acting antidepressants.

The search for new antidepressants agents has intensified in recent years. Indeed, sulfur compounds have performed as well as conventional antidepressant drugs in studies of depression, where they have been demonstrated to alter mood (Parcell 2002). Our research group has studied pharmacological properties of an organosulfur compound, ((4-*tert* butylcyclohexylidene) methyl) (4-methoxystyryl) sulfide (BMMS). This compound has showed antioxidant (Ianiski et al. 2014, 2017), antiaminesic (Da Silva et al. 2017) and antinociceptive (Ianiski et al. 2017) actions.

In view of our interest in searching new treatment alternatives for depression, as well as in investigating pharmacological properties of BMMS, the primary aim of the present study was to verify the antidepressant-like effect of BMMS in mice. The second objective was to evaluate the involvement of serotoninergic, glutamatergic and nitrergic systems in the antidepressant-like activity of BMMS. Finally, we also examined the contribution of enzymes monoamine oxidase (MAO) and Na^+, K^+-ATPase in prefrontal cortex of mice.

Materials and methods

Animals

Male adult Swiss mice (25–35 g) from a local breeding colony were used. Swiss mice were chosen based on previous studies that demonstrated antidepressant drug effect in this strain (Ripoll et al. 2003; David et al. 2003; Brocardo et al. 2008; Jesse et al. 2010; Brüning et al. 2011; Velasquez et al. 2017; Abreu et al. 2018; Bogatko et al. 2018; de Oliveira et al. 2018; Fajemiroye et al. 2018; Moretti et al. 2018; Sartim et al. 2019).

The animals were kept on a separate room, on a 12 h light/dark cycle, at a temperature of 22 ± 2 °C, with free access to food and water. All behavioral tests were carried out between 08.00 a.m. and 04.00 p.m. All experiments were performed on separate groups of animals and each animal was used only once in each test. Ethical Research Committee of the Federal University of Pelotas approved the present experimental study (number 8992–2017).

Drugs

BMMS (Fig. 1) was prepared according to the literature (Silveira et al. 2011). The chemical purity of the compound (99.9%) was determined by gas chromatography or high-performance liquid chromatography. Compound was diluted in canola oil. The following drugs were used: Fluoxetine (commercially purchased), ketanserin, ondansetron, WAY100635, MK-801 and L-arginine (Sigma Chemical Co, USA). These drugs were dissolved in saline. All drugs were administered in a constant volume of 10 ml/kg body weight. All other chemicals were of analytical grade and obtained from standard commercial suppliers.

Behavioral tests

All behavioral tests were scored by an observer-blinded, when the researcher does not know treatment that a mouse undergoes.

Dose-response curve of antidepressant-like action of BMMS in the forced swimming test (FST) and tail suspension test (TST)

To evaluate the dose-response curve of antidepressant-like action of BMMS, mice ($n = 7$ animals/group) were treated with BMMS (0.1, 1 and 10 mg/kg, by intragastric (i.g.) route), fluoxetine (32 mg/kg, i.g.) or canola oil (control, 10 ml/kg, i.g.) at 30 min before the FST or TST.

The FST was conducted using the method described by Porsolt et al. (1977). In this test, mice were individually forced to swim in an open cylindrical container (10 cm in diameter and 25 cm in height), containing 19 cm of water at 25 ± 1 °C. The duration of immobility was scored during a 6-min period by an experienced observer (Kaster et al. 2005). Each mouse was considered as immobile when floating motionless or making only those movements necessary to keep its head above

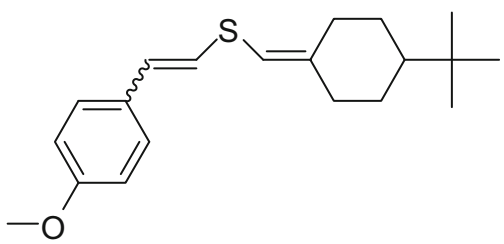

Fig. 1 Chemical structure of ((4-*tert*-butylcyclohexylidene) methyl) (4-methoxystyryl) sulfide (BMMS)

water. A decrease in the duration of immobility is an indicative of antidepressant-like effect.

The TST was conducted as described by Steru et al. (1985). Mice were suspended 50 cm above the ground by an adhesive tape placed approximately 1 cm from the tip of the animals tail. Mice were considered immobile only when they hung passively and completely motionless. Immobility time was manually recorded during a 6-min period by an experienced observer (Kaster et al. 2005). A decrease in the duration of immobility is an indicative of antidepressant-like effect.

Involvement of the 5-HT receptor subtypes on the antidepressant-like action of BMMS in the TST

To investigate the possible involvement of the 5-HT receptor subtypes on the antidepressant-like effect caused by BMMS on reducing the immobility time in the TST, independent groups of animals were pretreated with WAY100635 (0.1 mg/kg, subcutaneous (s.c.), a selective 5-HT_{1A} receptor antagonist), ketanserin (5 mg/kg, intraperitoneal (i.p.), a 5-$HT_{2A/2C}$ receptor antagonist) or ondasentron (1 mg/kg, i.p., a 5-HT_3 receptor antagonist). After 15 min of WAY100635 and ondansetron administrations or 30 min of ketanserin administration, mice received BMMS (10 mg/kg, i.g.) or canola oil (vehicle, 10 ml/kg, i.g.) and were tested in the TST 30 min later. TST was described above (item 2.3.1). The doses and times of treatments with 5-HT receptor antagonists were chosen based on previous studies, which did not modify the basal response in the TST and the locomotor activity (Zomkowski et al. 2004; Jesse et al. 2010; Brüning et al. 2011).

Involvement of the N-methyl-D-aspartate (NMDA) receptor on the antidepressant-like action of BMMS in the TST

To assess the possible involvement of the glutamatergic system on the antidepressant-like effect of BMMS in the TST, independent groups of animals were pretreated with MK-801 (0.01 mg/kg, i.p., a glutamate NMDA receptor antagonist). After 15 min, the mice received BMMS (10 mg/kg, i.g.) or canola oil (vehicle, 10 ml/kg, i.g.) and were tested in the TST 30 min later. TST was described above (item 2.3.1). The dose and time of treatment with MK-801 were chosen based on previous studies, which did not modify the basal response in the TST and the locomotor activity (Ostadhadi et al. 2016; Réus et al. 2016).

Involvement of the L-arginine-nitric oxide (NO) pathway on the antidepressant-like action of BMMS in the TST

The role played by the L-arginine-NO pathway on the antidepressant-like effect caused by BMMS in TST was investigated in different groups of animals. The mice were pretreated with L-arginine (500 mg/kg, i.p., a precursor of NO). Thirty minutes after L-arginine administration, BMMS (10 mg/kg, i.g.) or canola oil (vehicle, 10 ml/kg, i.g.) was administered. TST was carried out 30 min after the treatment with BMMS or vehicle. TST was described above (item 2.3.1). The dose and time of treatment with L-arginine were chosen based on previous studies, which did not change the basal response in the TST and the locomotor activity (Rosa et al. 2003; Liebenberg et al. 2015).

Effect of treatments on the spontaneous locomotor activity in the open-field test (OFT)

The spontaneous locomotor behavior was assessed in the OFT (Walsh and Cummins 1976). The OFT was carried out with the purpose of excluding sedative or motor abnormality after treatments with BMMS, fluoxetine, WAY100635, ketanserin, ondansetron, MK-801 or L-arginine. The open-field was made of plywood (30 cm in height × 45 cm in length × 45 cm in width) and divided by masking tape markers into 09 squares (3 rows of 3). Each animal was placed individually at the center of the apparatus and observed for 4-min period to record the locomotor (number of segments crossed with the four paws) and exploratory (expressed by the number of time rearing on the hind limbs) activities.

Ex vivo assays

MAO-A, MAO-B and Na^+, K^+-ATPase activities were performed to verify the involvement of these enzymes in the antidepressant-like effect of BMMS. Mice were pretreated with BMMS (10 mg/kg, i.g.) or canola oil (control, 10 ml/kg, i.g.), and after 30 min, the animals were died, and the prefrontal cortex was removed for analysis.

MAO activity assay

A preparation of brain mitochondria was used for MAO assay (Soto-Otero et al. 2001). The cerebral structures were removed and washed in ice-cold isolation medium (Na_2PO_4/KH_2PO_4 isotonized with sucrose, pH 7.4). Cerebral mitochondria were then obtained by differential centrifugation. Briefly, after removing blood vessels and pial membranes, prefrontal cortex was manually homogenized with 1:4 (*w*/*v*) of the isolation medium. Then, the homogenate was centrifuged at 900×g at 4 °C for 5 min. The supernatant was centrifuged at 12,500×g for 15 min. The mitochondria pellet was then washed once with isolation medium and recentrifuged under the same conditions. Finally, the mitochondrial pellet was reconstituted in a buffer solution (Na_2PO_4/ KH_2PO_4 isotonized with KCl, pH 7.4) and stored in aliquots.

MAO activity was determined according to Krajl (1965), with some modifications (Matsumoto et al. 1984). An aliquot of 100 μl of each sample was incubated at 37 °C for 5 min in a

medium containing buffer solution and specific inhibitors, selegiline (a MAO-B inhibitor, 250 nM) or clorgiline (a MAO-A inhibitor, 250 nM) at a final volume of 600 μl. Then 20 μl of kynuramine dihydrobromide was added to the reaction mixture (90 μM (MAO-A) and 60 μM (MAO-B)) as substrate. Samples were then incubated at 37 °C for 30 min. After incubation, the reaction was terminated by adding 10% trichloroacetic acid (TCA). After cooling and centrifugation at 3000×g for 15 min, an aliquot of 800 μl of the supernatant was added to 1 ml of 1 M NaOH. The fluorescence intensity was detected spectrofluorimetrically with excitation at 315 nm and emission at 380 nm. Clorgiline (100 nM) and selegiline (100 nM) were used as positive controls in MAO-A and MAO-B assays, respectively. The concentration of 4-hydroxyquinoline (4-OH quinoline) was estimated from a corresponding standard fluorescence curve of 4-OH quinoline. MAO activity was expressed as nmol 4-OH quinoline/mg protein/min.

Na^+, K^+-ATPase activity assay

The prefrontal cortex was homogenized in 50 mM Tris/HCl pH 7.5, 1:10 (*w*/*v*) and centrifuged at 4000×g for 10 min at 4 °C to yield a low-speed supernatant fraction (S1). A reaction mixture was used containing S1, 3 mM $MgCl_2$, 125 mM NaCl, 20 mM KCl and 50 mM Tris/HCl, pH 7.4, in a final volume of 500 μl. The reaction was initiated by the addition of ATP to a final concentration of 3.0 mM. Control samplings were performed under the same conditions with the addition of 0.1 mM ouabain. The samples were incubated at 37 °C for 30 min and the incubation was stopped by adding 10% TCA with 10 mM $HgCl_2$. Na^+, K^+-ATPase activity was calculated by the difference between the two assays. Released inorganic phosphate (Pi) was measured by the method of Fiske and Subbarow (1925). Enzyme activity was expressed as nmol Pi/mg protein/min.

Protein determination

The protein concentration was measured by the method of Bradford (1976), using bovine serum albumin as the standard.

Statistical analysis

The normality of data was evaluated by the D'Agostino and Pearson omnibus normality test. The data were analyzed by one-way or two-way analysis of variance (ANOVA) followed by Newman-Keuls test. For ex vivo assays, the data were analyzed using a non-paired t-test. All analyses were performed using the GraphPad software (GraphPad software, San Diego, CA, USA). Data were expressed as mean ± standard error of the mean (S.E.M.). Probability values less than ($p < 0.05$) were considered statistically significant.

Results

Dose-response curve of antidepressant-like action of BMMS in the FST and TST

The immobility time in the FST and TST of animals treated with BMMS is shown in Fig. 2a and b, respectively. According to the results the doses of 0.1, 1 and 10 mg/kg of BMMS decreased the immobility time of mice in the FST (One-way ANOVA + Newman-Keuls test: $F_{(4,30)} = 36.96$, $p < 0.0001$) and in the TST (One-way ANOVA + Newman-Keuls test: $F_{(4,30)} = 41.20$, $p < 0.0001$), in comparison to the control group. The fluoxetine (32 mg/kg) also caused a decrease in the immobility time in the FST (Fig. 2a) and TST (Fig. 2b), when compared to the control group.

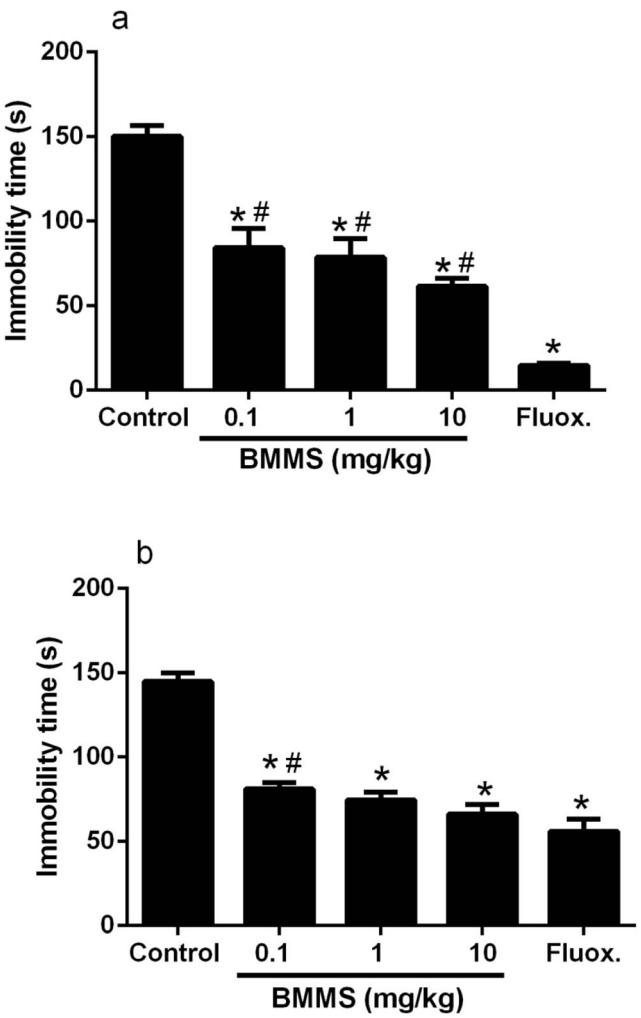

Fig. 2 Effect of ((4-*tert*-butylcyclohexylidene) methyl) (4-methoxystyryl) (BMMS) (0.1–10 mg/kg) and fluoxetine (Fluox) (32 mg/kg) in the immobility time in the FST (**a**) and TST (**b**) in mice. Values are expressed as mean ± standard error of the mean (S.E.M.) ($n = 7$). (*) denotes $p < 0.05$ as compared to the control group and (#) denotes $p < 0.05$ as compared to the Fluox treated group (one-way ANOVA followed by Newman-Keuls test)

Involvement of the 5-HT receptor subtypes on the antidepressant-like action of BMMS in the TST

Results depicted in Fig. 3a show that the pretreatment of mice with WAY100635 (a 5-HT_{1A} receptor antagonist) prevented the antidepressant-like effect of BMMS (10 mg/kg) in TST (Two-way ANOVA + Newman-Keuls test; BMMS: $F_{(1,24)} = 31.70$, $p < 0.0001$; WAY100635: $F_{(1,24)} = 12.85$, $p = 0.0015$; interaction: $F_{(1,24)} = 16.17$, $p = 0.0005$).

As shown in Fig. 3.b the pretreatment of mice with, ketanserin (a 5-$HT_{2A/2C}$ receptors antagonist) prevented the antidepressant-like effect of BMMS (10 mg/kg) in TST (Two-way ANOVA + Newman-Keuls test; BMMS: $F_{(1,24)} = 13.32$, $p = 0.0013$; ketanserin: $F_{(1,24)} = 22.93$, $p < 0.0001$; interaction: $F_{(1,24)} = 6.975$, $p = 0.0143$).

Pretreatment of mice with ondansetron (a 5-HT_3 receptor antagonist) (Fig. 3c) partially prevented the antidepressant-like effect of BMMS (10 mg/kg) in TST (Two-way ANOVA + Newman-Keuls test; BMMS: $F_{(1,24)} = 55.96$, $p < 0.0001$; ondansetron: $F_{(1,24)} = 1.456$, $p = 0.2394$; interaction: $F_{(1,24)} = 3.382$, $p = 0.0783$).

Involvement of the N-methyl-D-aspartate (NMDA) receptor on the antidepressant-like action of BMMS in the TST

Results depicted in Fig. 4. show that the pretreatment of mice with MK-801 (a non-competitive NMDA antagonist) did not reverse the reduction in immobility time elicited by BMMS (10 mg/kg) in TST (Two-way ANOVA + Newman-Keuls test; BMMS $F_{(1,24)} = 48.23$, $p < 0.0001$; MK-801: $F_{(1,24)} = 3.022$, $p = 0.0950$; interaction: $F_{(1,24)} = 0.4124$, $p = 0.5268$).

Involvement of the L-arginine-nitric oxide (NO) pathway on the antidepressant-like action of BMMS in the TST

The results depicted in Fig. 5. show that the pre-treatment with L-arginine (a NO precursor) partially prevented the antidepressant-like effect of BMMS (10 mg/kg) in the TST (Two-way ANOVA + Newman-Keuls test; BMMS: $F_{(1,24)} = 115.7$, $p < 0.0001$; L-arginine: $F_{(1,24)} = 33.47$, $p < 0.0001$; interaction: $F_{(1,24)} = 8.476$, $p = 0.0077$).

Effect of treatments on the spontaneous locomotor activity in the open-field test (OFT)

BMMS, at all doses tested, did not produce any change in the number of crossings and rearing of the mice submitted to the OFT (Table 1). In addition, the administration of WAY100635, ketanserin, ondansetron, MK-801 or L-arginine and/or BMMS did not cause any change in the locomotor and exploratory activities assessed in the OFT (Table 1).

Ex vivo assays

MAO activity assay

As shown in Fig. 6a, BMMS (10 mg/kg) selectively inhibited the MAO-A activity in the prefrontal cortex (Non-paired T-test; df = 12; t = 2.762, $p = 0.0172$). On the other hand, the compound was not able to inhibit the activity of MAO-B (Non-paired T-test; df = 12; t = 1.625, $p = 0.1300$) (Fig. 6b) in prefrontal cortex of mice.

Na^+, K^+-ATPase activity assay

As verified in Fig. 7, the results demonstrated that BMMS treatment (10 mg/kg) increased the activity of the Na^+, K^+-ATPase in prefrontal cortex of mice (Non-paired T-test; df = 10, t = 5.773, $p = 0.0002$).

Discussion

The present study showed, for the first time, that BMMS, produced a significant antidepressant-like effect in mice. Moreover, results indicated the involvement of serotonin and L-arginine-NO pathways in this effect. Importantly, BMMS was a selective inhibitor of cerebral cortical MAO-A activity, interacting with monoaminergic system. In addition, compound increased Na^+, K^+-ATPase activity in the prefrontal cortex, demonstrating the involvement of this enzyme in the antidepressant-like effect of the BMMS. In this context, our results inferred that BMMS is a multi-target compound (Fig. 8).

BMMS, at low doses (0.1–10 mg/kg) was able to cause an antidepressant-like effect in TST and FST in mice. In addition, drugs used in the treatment of depression have demonstrated a reduction in the immobility time in these tests (Porsolt et al. 1977). In this way, our results demonstrated that the administration of fluoxetine (32 mg/kg), a positive control, produced an antidepressant-like action in FST and TST.

Numerous neural pathways have been involved in the pathophysiology of depression (Altamura et al. 2008). Indeed, the involvement of isolated systems in depression has been well-described, mainly serotonergic pathway (Wong and Licinio 2001; Mann 2003; Goncalves et al. 2012). However, there are mutual interactions between 5-HT and NO in a specific physiological and/or pathological condition, since NO increases the release of 5-HT and inhibits its reuptake (Jesse et al. 2008). The use of inhibitors of nitric oxide synthase (NOS), an important enzyme for NO synthesis, accentuated the effect of antidepressants already used in the clinic (Rosa et al. 2003). Importantly, neuronal nitric oxide synthase (nNOS), is expressed by a subset of 5-HT neurons in the dorsal raphe (Johnson and Ma 1993; Tagliaferro et al. 2001).

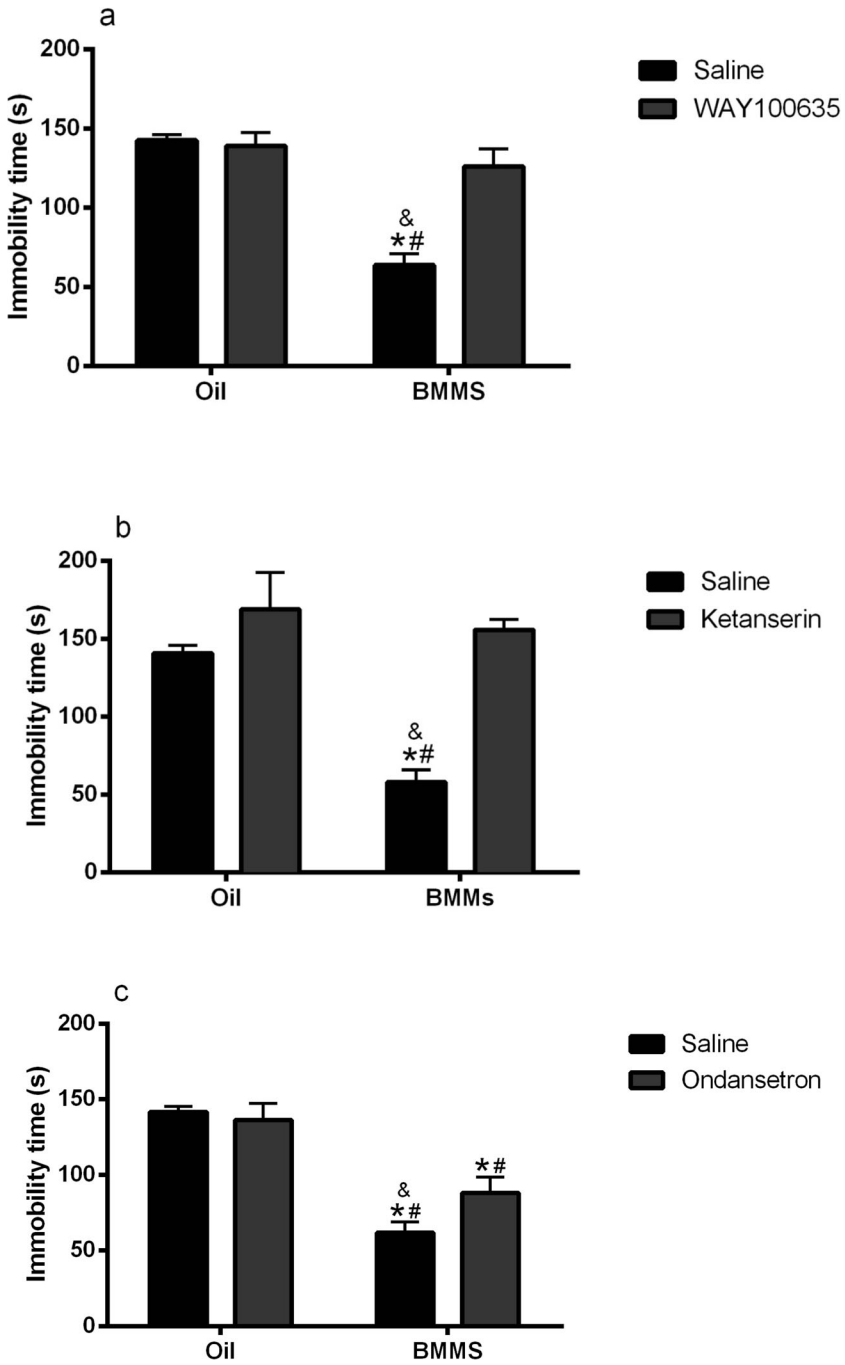

Fig. 3 Effect of WAY100635 (0.1 mg/kg, s.c.) (**a**), ketanserin (5 mg/kg, i.p.) (**b**) and ondansetron (1 mg/kg, i.p.) (**c**) in mice in the TST. Values are expressed as mean ± standard error of the mean (S.E.M.) (n = 7). (*) denotes $p < 0.05$ as compared to the control group, (#) denotes $p < 0.05$ as compared to the BMMS group and (&) denotes $p < 0.05$ as compared to the antagonist group (two-way ANOVA followed by Newman-Keuls test)

In this sense, antidepressant-like actions caused by NOS inhibitors are dependent on endogenous 5-HT, since inhibition of 5-HT synthesis blocked the antidepressant-like effects induced by systemic treatment with these drugs (Harkin et al. 2003).

In this context, this study investigated if serotonergic (through administration of different 5-HT receptor antagonists) and nitrergic (through administration of a precursor of NO) pathways are involved in the antidepressant-like action of BMMS. Our results showed the involvement of both systems, since administration of 5-HT_{1A} (WAY100635) and 5-$HT_{2A/2C}$ (ketanserin) receptor antagonists abolished the antidepressant-like action of BMMS, while a 5-HT_3-receptor antagonist (ondansetron) and a NO precursor (L-arginine) partially abolished the antidepressant-like action of the compound. As the molecular and neurochemical aspects are not yet well known, we can not affirm exactly how BMMS interferes in the serotonergic and nitrergic pathways, but this study strongly indicates the involvement of these pathways in the antidepressant-like effect of compound.

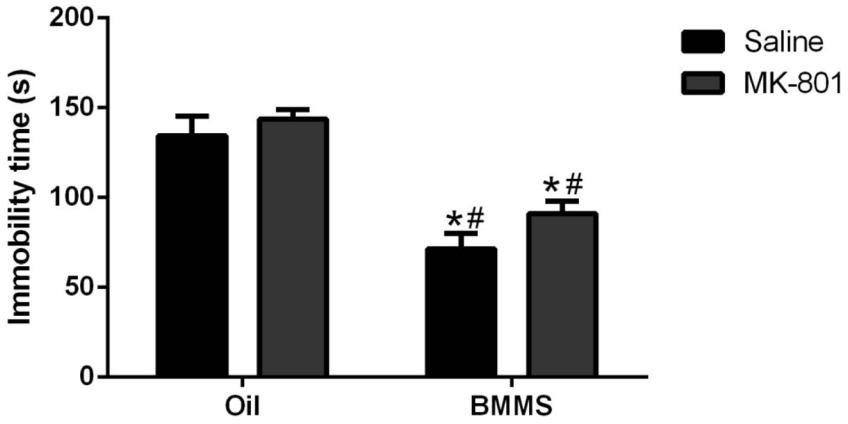

Fig. 4 Effect of MK-801 (0.01 mg/kg, i.p.) in mice in the TST. Values are expressed as mean ± standard error of the mean (S.E.M.) (n = 7). (*) denotes $p < 0.05$ as compared to the control group, (#) denotes $p < 0.05$ as compared to the BMMS group and (&) denotes $p < 0.05$ as compared to the MK-801 group (two-way ANOVA followed by Newman-Keuls test)

In addition, the glutamatergic theory postulates that glutamate can shape the risk of depression by influencing neuronal fate (neurotoxicity) or the unfolding of new neural networks (neuroplasticity). Indeed, NMDA receptor may be the target of some antidepressants, and glutamatergic system plays an important role in pathophysiology of depression (Haj-Mirzaian et al. 2015). NMDA activation is also known to increase neuronal nitric oxide synthase (nNOS) activity, increasing NO synthesis, mediating several behavioral responses to stress (Guimarães et al. 2005; Joca et al. 2015). For instance, systemic and intra-cerebral administration of NMDA antagonists or nNOS inhibitors induces antidepressant-like effect in different stress-based animal models (Joca et al. 2015).

Considering relationship between the serotonergic and nitrergic system and the glutamatergic one, we evaluated the involvement of the glutamatergic system in the action of compound. Our results demonstrated that the NMDA receptor does not seem to be directly involved in the antidepressant-like effect of BMMS, which does not totally exclude the involvement of the glutamatergic system and NMDA receptor in the antidepressant-like effect of the compound. More studies are needed to investigate the glutamatergic system as a whole.

In addition, studies indicated that MAO inhibitors (MAOIs) also are being effective in the depression treatment (Wong and Licinio 2001; Elhwuegi 2004). MAO, a mitochondrial enzyme, exists as two isoforms: MAO-A and MAO-B that differ in tissue distribution and in the type of metabolized monoamine (Shih et al. 1999). MAO has a role in degradation of the monoamines in the brain (Meyer et al. 2006) and its inactivation blocks catabolism of these neurotransmitters, increasing their concentrations in the synaptic cleft (Finberg and Rabey 2016). MAO-A is part of 5-HT system along with 5-HT transporters and 5-HT receptors. MAO-A inhibitors inhibit MAO-A catalytic activity, resulting in an elevated 5-HT concentration in the brain (Finberg and Rabey 2016; Fišar 2016). A significant increase in the levels of MAO-A is found in association with the pathogenesis of major depressive disorder (Meyer et al. 2006, 2009). Mechanistic details showed that stress-induced MAO-A expression is mediated by transcription factors, in particular, kruppel like factor 11 (KLF11) (also referred to as transforming growth factor-β-inducible early gene 2 (TIEG2)) (Grunewald et al. 2012; Harris et al. 2015; Higuchi et al. 2017). Previous evidence has characterized KLF11 as a transcriptional regulator of MAO-A (Grunewald et al. 2012). It has been suggested that KLF11 can mediate glucocorticoid-induced up-regulation of MAO-A mRNA, protein, enzymatic activities owing to the fact that (1) glucocorticoids increase KLF11 mRNA and protein levels, (2) KLF11 overexpression increases MAO-A gene expression levels and enzymatic activity, which is further promoted by

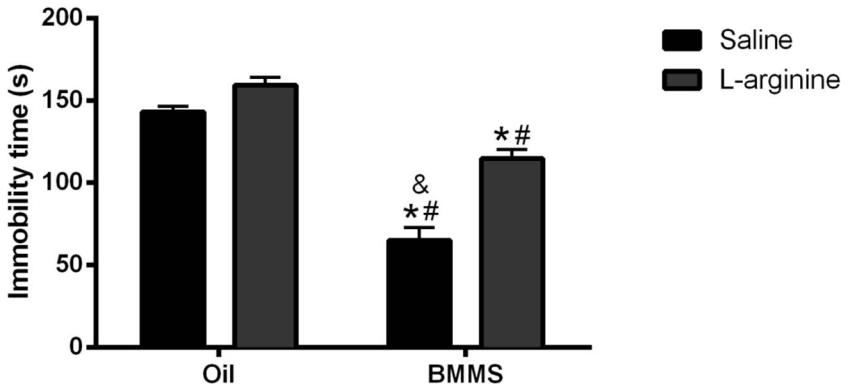

Fig. 5 Effect of L-arginine (500 mg/kg, i.p.) in mice in the TST. Values are expressed as mean ± standard error of the mean (S.E.M.) (n = 7). (*) denotes $p < 0.05$ as compared to the control group, (#) denotes $p < 0.05$ as compared to the BMMS group and (&) denotes $p < 0.05$ as compared to the L-arginine group (two-way ANOVA followed by Newman-Keuls test)

glucocorticoids, while KLF11 knockdown mediated by si-RNA decrease the MAO-A gene expression and enzymatic activity (Grunewald et al. 2012). It is also reported that glucocorticoids induce the translocation of the KLF11 protein from cytosol to the nucleus (Grunewald et al. 2012), although the molecular mechanism of the translocation remains unknown.

Here, a single administration of BMMS (10 mg/kg) was effective to selectively inhibit the MAO-A activity in prefrontal cortex of mice. On the other hand, the compound had no effect in the MAO-B activity. In fact, MAOIs are considered effective in rodent models (Pesarico et al. 2015) and in humans (Kahn et al. 1989), since they have an antidepressant effect. Our results indicate that BMMS is a selective inhibitor of the MAO-A enzyme, demonstrating that this effect may directly contribute to the antidepressant-like effect of compound in mice. This is an important advantage of BMMS in relation to antidepressant drugs used in the clinic, given that these drugs present marked side effects due to lack of selectivity for the MAO-A isoform.

Studies have shown that selective inhibition of MAO-A activity can occur due to differences in the three-dimensional arrays and substrate binding sites of MAO-A isoforms (Medvedev et al. 1996; Tsugeno et al. 1995). MAO-A has a similar affinity for most substrates with aromatic rings, but difference in the affinity among substrates was observed for MAO-B (Tsugeno and Ito 1997). In addition, the participation of the aromatic side chain in MAO-A substrate recognition was evidenced, which suggests that the π-π interaction between the aromatic rings of the enzyme and the substrates is considered of extreme importance to explain the affinity of MAO-A for aromatic substrates (Tsugeno et al. 1995). In this way, the selective inhibition of MAO-A activity by BMMS can be attributed to the participation of its aromatic side chain with the MAO-A substrate, in addition to the fact that the BMMS has π-systems conjugated in its chemical structure could explain its MAO-A selective affinity.

In addition, we evaluated the effect of BMMS on Na^+, K^+ -ATPase activity in an attempt to correlate its antidepressant-like effect with the activity of this enzyme. The Na^+, K^+-ATPase is crucial for various cellular functions, such as maintaining electrochemical gradients necessary for neuronal activity, through the active exchange of intracellular Na^+ ions by

Table 1 Effect of fluoxetine, BMMS administration and its combined treatment with serotonin antagonists, NMDA antagonist or NO precursor on spontaneous locomotor and exploratory activities in mice

Group	Crossing	Rearing
Control	85.0 ± 4.8	32.8 ± 2.7
BMMS 0.1 mg/kg	84.0 ± 5.3	34.4 ± 1.5
BMMS 1 mg/kg	91.2 ± 5.9	36.2 ± 1.7
BMMS 10 mg/kg	93.7 ± 2.7	35.1 ± 2.0
Fluoxetine	92.0 ± 8.3	33.2 ± 3.1
WAY100635	93.1 ± 1.8	40.0 ± 3.5
Ketanserin	74.6 ± 5.8	31.8 ± 4.9
Ondansetron	97.5 ± 1.2	41.3 ± 3.4
MK-801	84.8 ± 5.4	31.8 ± 2.8
L-arginine	95.5 ± 7.7	34.0 ± 4.8
BMMS + WAY100635	96.5 ± 2.8	36.1 ± 1.7
BMMS + Ketanserin	69.0 ± 8.9	25.0 ± 3.2
BMMS + Ondansetron	98.1 ± 1.8	34.3 ± 6.1
BMMS + MK-801	84.5 ± 3.0	34.7 ± 4.1
BMMS + L-arginine	110.5 ± 6.0	37.5 ± 2.8

Values are expressed as mean ± standard error of the mean (S.E.M) (n = 6–7). One-way ANOVA followed by Newman-Keuls test for BMMS and fluoxetine. Two-way ANOVA for BMMS + antagonist or NO precursor, followed by Newman-Keuls test

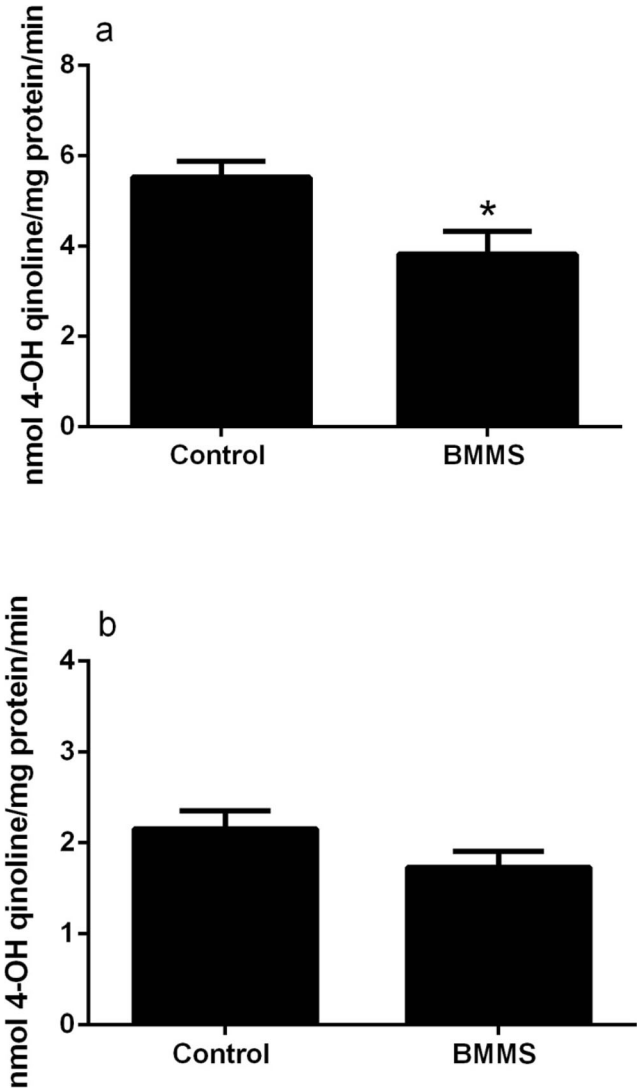

Fig. 6 Effect of ((4-*tert*-butylcyclohexylidene) methyl) (4-methoxystyryl) (BMMS) on monoamine oxidase (MAO)-A (**a**) and MAO-B (**b**) activities, in the prefrontal cortex in mice. Values are expressed as mean ± standard error of the mean (S.E.M.) (n = 7). (*) denotes $p < 0.05$ as compared to the control group (one-way ANOVA followed by T test)

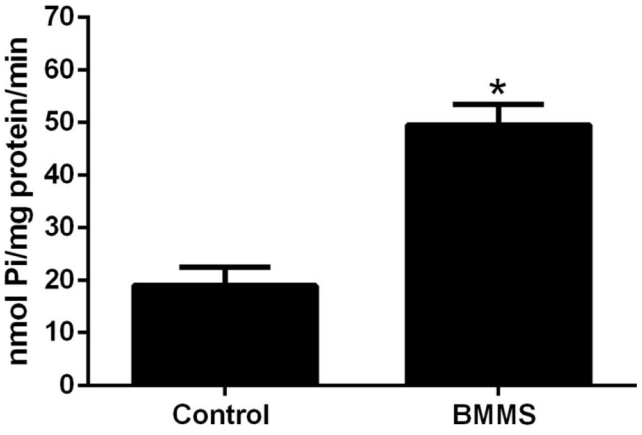

Fig. 7 Effect of ((4-*tert*-butylcyclohexylidene) methyl) (4-methoxystyryl) (BMMS) on Na^+, K^+-ATPase activities, in the prefrontal cortex in mice. Values are expressed as mean ± standard error of the mean (S.E.M.) (n = 6). (*) denotes $p < 0.05$ as compared to the control group (one-way ANOVA followed by T test)

extracellular K^+ ions (Shamraj and Lingrel 1994). Genetic mutations resulting in decreased neuronal Na^+, K^+-ATPase activity may put individuals at risk for depression given that decreased Na^+, K^+-ATPase activity is observed in depressive disorders and animal models of depression (Gamaro et al. 2003; de Vasconcellos et al. 2005; Goldstein et al. 2006; Crema et al. 2010). In this context, Na^+, K^+-ATPase α3 gene expression is decreased in major and bipolar depression in the prefrontal cortex (Tochigi et al. 2008). In addition, Kirshenbaum et al. (2011) observed an interesting correlation between Na^+, K^+-ATPase activity and mood that may relate to both unipolar depression and bipolar disorder in Na^+, K^+-ATPase α3 heterozygous mice (Atp1a3±). Moreover, data in the literature show that changes in the serotonergic system, such as 5-HT levels, may compromise enzyme activity (Carfagna et al. 1996). 5-HT is removed of the synaptic cleft by the transporters located in the presynaptic neurons through Na^+ dependent capitation, which is directly related to the activity of the enzyme Na^+, K^+-ATPase (Lesch et al. 1993). In

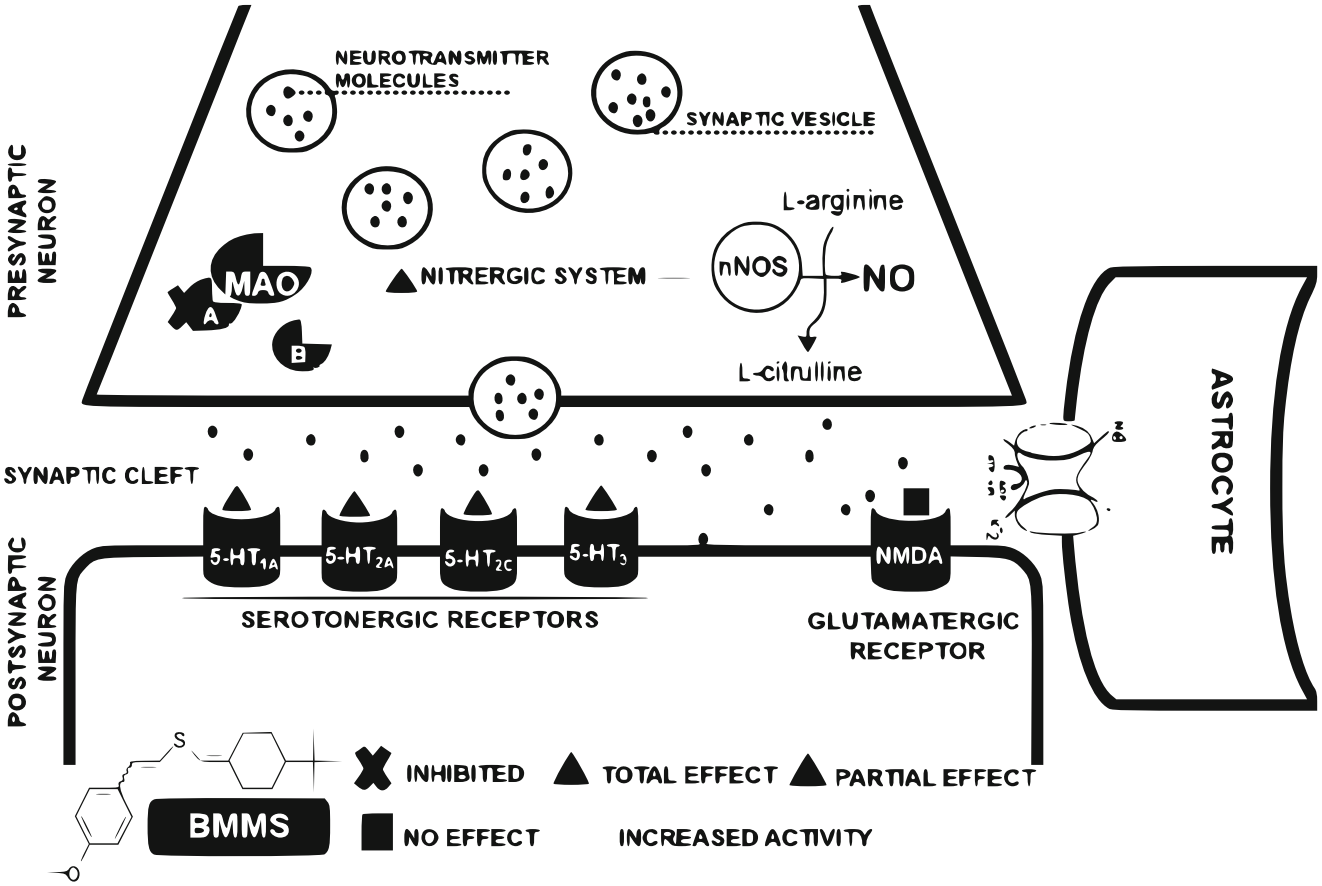

Fig. 8 Summary of action mechanism of the antidepressant-like effect of ((4-tert-butylcyclohexylidene) methyl) (4-methoxystyryl) sulfide (BMMS). Our results have inferred that BMMS is a multi-target compound, since several systems may be involved in the effect of this compound. BMMS modulated the 5-HT_{1A}, 5-$HT2_{A/2C}$ and 5-HT_3 receptors, suggesting the involvement of serotonergic pathway in the antidepressant-like action of compound. The nitrergic pathway also appears to be involved in the effect of BMMS by modulating the nitric oxide precursor. On the other hand, BMMS was not able to act on the glutamatergic pathway through the NMDA receptor. According to the results ex vivo, BMMS was able to inhibit MAO-A enzyme activity, but did not alter MAO-B activity. In addition, the BMMS was able to act on the Na^+, K^+-ATPase enzyme by increasing its activity

the present study, our results showed that BMMS increased Na^+, K^+-ATPase activity in prefrontal cortex of mice, contributing to the antidepressant-like action of this compound.

It is important to emphasize that none of the treatments caused changes in the spontaneous locomotor and exploratory activities of the mice, indicating that anti-immobility effect of BMMS cannot be due nonspecific changes, such as psychostimulant activity. In this way, this is an important result given that psychostimulant drugs may give a false positive result in animal models, such as the FST and TST (Cryan et al. 2005).

In conclusion, our study demonstrated that BMMS exerted an antidepressant-like effect in the FST and TST in mice. The results also showed that serotonergic and nitrergic systems are involved in the antidepressant-like action of compound. According to ex vivo results, BMMS inhibited the MAO-A activity and increased the Na^+, K^+-ATPase activity. Our results inferred that BMMS is a multi-target compound, but further studies are needed to elucidate the other mechanisms of action and the contribution of other neurotransmission systems to antidepressant-like action of BMMS.

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