Progress in Neuro-Psychopharmacology & Biological Psychiatry 34 (2010) 294–302

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Evidence for the involvement of the serotonergic 5-$HT_{2A/C}$ and 5-HT_3 receptors in the antidepressant-like effect caused by oral administration of bis selenide in mice

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ARTICLE INFO

Article history:
Received 4 July 2009
Received in revised form 26 November 2009
Accepted 26 November 2009
Available online 2 December 2009

Keywords:
Antidepressant
Bis selenide
Noradrenergic
Selenium
Serotonergic and dopaminergic receptors

ABSTRACT

The present study investigated a possible antidepressant-like activity of bis selenide using two predictive tests for antidepressant effect on rodents: the forced swimming test (FST) and the tail suspension test (TST). Bis selenide (0.5–5 mg/kg, p.o.) decreased the immobility time in the mouse FST and TST. The anti-immobility effect of bis selenide (1 mg/kg, p.o.) in the TST was prevented by the pretreatment of mice with p-chlorophenylalanine methyl ester (PCPA; 100 mg/kg, i.p., an inhibitor of serotonin synthesis), ketanserin (1 mg/kg, i.p., a 5-$HT_{2A/2C}$ receptor antagonist), and ondasentron (1 mg/kg, i.p., a 5-HT_3 receptor antagonist). Pretreatment of mice with prazosin (1 mg/kg, i.p., an α_1-adrenoceptor antagonist), yohimbine (1 mg/kg, i.p., an α_2-adrenoceptor antagonist), propranolol (2 mg/kg, i.p., a β-adrenoceptor antagonist), SCH23390 (0.05 mg/kg, s.c., a dopamine D_1 receptor antagonist), sulpiride (50 mg/kg, i.p., a dopamine D_2 receptor antagonist), or WAY 100635 (0.1 mg/kg, s.c., a selective 5-HT_{1A} receptor antagonist) did not block the antidepressant-like effect of bis selenide (1 mg/kg, p.o.) in the TST. Administration of bis selenide (0.1 mg/kg, p.o.) and fluoxetine (1 mg/kg), at subeffective doses, produced an antidepressant-like effect in the TST. Bis selenide did not alter Na^+ K^+ ATPase, MAO-A and MAO-B activities in whole brains of mice. Bis selenide produced an antidepressant-like effect in the mouse TST and FST, which may be related to the serotonergic system (5-$HT_{2A/2C}$ and 5-HT_3 receptors).

1. Introduction

Depression is a common illness associated with high rates of chronicity, relapse, and recurrence, psychosocial and physical impairments and suicide. Depression is also considered a significant risk factor for the development of coronary artery disease and stroke (Musselman et al., 1998). Regarding treatment, about 65% of patients ultimately respond to antidepressant drug therapy (Steffens et al., 1997), which has numerous side effects associated (Nemeroff and Owens, 2002).

Although the molecular alterations underlying the pathogenesis of depression remain to be clearly established, preclinical and clinical studies have suggested the involvement of monoamines, particularly serotonergic and noradrenergic systems (Millan, 2004). There are evidences indicating that serotonergic and noradrenergic neurotransmissions are involved in the expression of an antidepressant-like effect in the behavioral despair models of depression (Elhwuegi, 2004). Moreover, pharmacological studies have reported the efficacy of antidepressants with dopaminergic effects on the treatment of depression (Papakostas, 2006) as well as antidepressant-like responses in preclinical models of depression (D'Aquila et al., 2000).

Monoamine oxidase (MAO) is the key enzyme that is associated with the metabolism of these monoamines regulating their intracellular concentrations in the brain. Therefore, the abnormal function of this enzyme is thought to be involved in several psychiatric disorders, such as depression (Deniker, 1983). Na^+ K^+ ATPase is the enzyme responsible for the active transport of sodium and potassium ions in the nervous system, maintaining the ionic gradient necessary for neuronal excitability and regulation of neuronal cell volume. Moreover, its activity is decreased in patients with bipolar affective disorder and other psychiatric disorders (Reddy et al., 1992; El-Mallakh and Wyatt, 1995). Some studies have reported that psychoactive drugs such as haloperidol, carbamazepine, and lithium modify Na^+ K^+ ATPase activity (Reddy et al., 1992; El-Mallakh and Wyatt, 1995). The clinical therapy of depression is based on classical antidepressant drugs such as monoamine oxidase inhibitors (MAOi; e.g. tranylcypromine), catecholamine reuptake inhibitors (e.g. imipramine), and selective inhibitors of serotonin reuptake (SSRIs; e.g. fluoxetine) (Wong and Licinio, 2001).

Abbreviations: ANOVA, analysis of variance; bis selenide, [(*Z*)-2,3-Bis(4-chlorophenylselanyl)prop-2-en-1-ol]; DA, dopamine; DMSO, dimethylsulfoxide; FST, forced swimming test; 5-HT, serotonin; i.p., intraperitoneal; MAO, monoamine oxidase; MAOi, monoamine oxidase inhibitors; NA, noradrenaline; NE, norepinephrine; OFT, open field test; PCPA, p-chlorophenylalanine methyl ester; p.o., per oral; SCH23390, (R)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TST, tail suspension test; WAY100635, N-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-N-(2-pyridynyl) cyclohexanecarboxamide.

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doi:10.1016/j.pnpbp.2009.11.023

Several studies have demonstrated the role of selenium in mood disorders (Hawkes and Hornbostel, 1996; Burk, 2002; Sher, 2008). The low-selenium status (low-selenium diet contains 32–36 μg per day) has been associated with a significant increased incidence of depression, anxiety, confusion, and hostility. In addition, high dietary and/or supplementary selenium (226 μg per day) improve mood (Rayman, 2000). Under this point of view, bis selenide, an organo-selenium compound, could be an attractive target for the treatment of depression because it is a non-toxic drug when acutely administered to rodents at doses with pharmacological effects (Savegnago et al., 2006, Jesse et al., 2007, 2008).

Considering the need of discovering compounds that could improve conventional therapies, we sought to investigate the effect of a single oral administration of bis selenide in the TST and FST, which are two animal models of depression used to screen new antidepressant drugs (Bourin et al., 2005). The positive results obtained in the TST have prompted us to investigate the involvement of the monoaminergic system in the antidepressant-like effect of bis selenide in this model. The next step of our study was to investigate the possible antidepressant-like effect of subeffective doses of bis selenide and conventional antidepressants in the TST. The activity of Na^+, K^+ ATPase, MAO-A, and MAO-B has been implicated in the pathogenesis of depression. Therefore, we also investigate the activity of Na^+, K^+ ATPase, MAO-A, and MAO-B in mice treated with bis selenide.

2. Materials and methods

2.1. Animals

The behavioral experiments were conducted using male adult Swiss mice (25–35 g) maintained at 22–25 °C with free access to water and food, under a 12:12 h light/dark cycle, with lights on at 6:00 a.m. All manipulations 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. The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, the Federal University of Santa Maria, Brazil. All efforts were made to minimize animals suffering and to reduce the number of animals used in the experiments.

2.2. Chemicals

Bis selenide [(*Z*)-2,3-Bis(4-chlorophenylselanyl)prop-2-en-1-ol] was prepared and characterized in our laboratory by the method previously described (Moro et al., 2005). Analysis of the ^{1}H NMR and ^{13}C NMR spectra showed analytical and spectroscopic data in full agreement with its assigned structure. The chemical purity of bis selenide (99.9%) was determined by GC/HPLC. The following drugs were used: prazosin, yohimbine, propranolol, SCH 23390, sulpiride, PCPA, WAY 100635, ketanserin, ondansetron, fluoxetine, imipramine, ATP, ouabain, selegiline, clorgiline, kynuramine and 4- hydroxyquinoline (Sigma Chemical Co, USA). Drugs were diluted in saline 0.9%. All other chemicals were of analytical grade and obtained from standard commercial suppliers.

2.3. In vivo experiments

To assess time-course of the antidepressant-like effect of bis selenide, mice were pretreated with bis selenide (5 mg/kg, p.o.) or vehicle (canola oil, 10 ml/kg, p.o.) 0.5–8 h before the TST. In order to assess the antidepressant-like effect of bis selenide, this compound (dose range: 0.1–5 mg/kg, p.o.) or vehicle was administered 1 h before the FST or TST. The doses of antagonists, which demonstrate effect on pharmacological and biochemical studies, and the doses of antidepressants, which did not modify the basal response in the TST and the locomotor activity in the OFT, were chosen on the basis of published studies. Several authors confirm the selectivity and efficacy of the above mentioned treatments at the doses used (Kaster et al., 2007; Brocardo et al., 2008; Cunha et al., 2008; Kulkarni et al., 2008; Binfaré et al., 2009).

To test the hypothesis that the antidepressant-like effect of bis selenide is mediated through an interaction with the noradrenergic system, animals were pretreated with prazosin (vehicle, 1 mg/kg, i.p., an α_1-adrenoceptor antagonist), yohimbine (vehicle, 1 mg/kg, i.p., an α_2-adrenoceptor antagonist) or propranolol (vehicle, 2 mg/kg, i.p., a β-adrenoceptor antagonist) and after 1 h, animals received bis selenide (1 mg/kg, p.o.) or vehicle and were tested in the TST 1 h later.

To assess the possible involvement of the dopaminergic system in the antidepressant-like effect of bis selenide in the TST, independent groups of animals were pretreated with SCH23390 (vehicle, 0.05 mg/kg, subcutaneous (s.c.), a dopaminergic D_1 receptor antagonist) or sulpiride (vehicle, 50 mg/kg, i.p., a dopaminergic D_2 receptor antagonist) and after 1 h, they received bis selenide (1 mg/kg, p.o.) or vehicle and were tested in the TST 1 h later.

To investigate the possible contribution of the serotonergic system to the effect of bis selenide on reducing the immobility time in the TST, animals were pretreated with PCPA (vehicle, 100 mg/kg, i.p., an inhibitor of serotonin synthesis), once a day, for 3 consecutive days. Twenty-four hours after the last PCPA injection, animals were treated with bis selenide (1 mg/kg, p.o.) or vehicle and were tested in the TST. In a separate series of experiments, the involvement of the serotonin (5-HT) receptor subtypes in the effect caused by bis selenide in the TST was studied. Mice were pretreated with WAY (vehicle, 0.1 mg/kg, s.c., a selective 5-HT_{1A} receptor antagonist), ketanserin (vehicle, 1 mg/kg, i.p., a 5-$HT_{2A/2C}$ receptor antagonist) or ondasentron (vehicle, 1 mg/kg, i.p., a 5-HT_3 receptor antagonist) and after 15 min they received bis selenide (1 mg/kg, p.o.) or vehicle and were tested in the TST 1 h later.

We investigated the antidepressant-like effect of subeffective doses of bis selenide with conventional antidepressants on the TST. To this end, mice received by p.o. route fluoxetine (vehicle, 1 mg/kg, a 5-HT reuptake inhibitor), imipramine (vehicle, 0.1 mg/kg, a 5-HT and noradrenaline reuptake inhibitor) and immediately after bis selenide (0.1 mg/kg, p.o.) or vehicle was administered. Sixty minutes later, the TST was carried out.

The open field test (OFT) was carried out to rule out any psychostimulant effect of the interaction of prazosin, yohimbine, propranolol, SCH 23390, sulpiride, PCPA, WAY 100635, ketanserin, ondasentron, fluoxetine, imipramine and bis selenide. These behavioral tests were performed by an observer blind to the drug treatment.

2.3.1. Forced swimming test (FST)

The test was conducted using the method described by Porsolt et al. (1977). Briefly, mice were individually forced to swim in open cylinders (25 cm height × 10 cm diameter) containing 19 cm of water at 25 ± 1 °C. The duration of immobility was scored during the 6 min test period as described previously (Rodrigues et al., 2002). Each mouse was recorded as immobile when floating motionless or making only those movements necessary to keep its head above water.

2.3.2. Tail suspension test (TST)

The total duration of immobility induced by tail suspension was measured according to the method described by Steru et al. (1985). Mice both acoustically and visually isolated were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during a 6-min period (Rodrigues et al., 2002).

2.3.3. Open field test (OFT)

The OFT was carried out to determine if the compounds or combination of compounds produced effects on locomotor and exploratory activities. The open field was made of polywood and