European Journal of Pharmacology 658 (2011) 145–149

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Behavioural Pharmacology

Antidepressant-like effect of *m*-trifluoromethyl-diphenyl diselenide in the mouse forced swimming test involves opioid and serotonergic systems

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ARTICLE INFO

Article history:
Received 28 October 2010
Received in revised form 1 February 2011
Accepted 17 February 2011
Available online 1 March 2011

Keywords:
Organoselenium
Antidepressant-like
Serotonin
Opioid
Depression
Selenium

ABSTRACT

Serotonergic and opioid systems have been implicated in major depression and in the action mechanism of antidepressants. The organoselenium compound *m*-trifluoromethyl-diphenyl diselenide (m–CF_3–$PhSe)_2$ shows antioxidant and anxiolytic activities and is a selective inhibitor of monoamine oxidase A activity. The present study was designed to investigate the antidepressant-like effect of (m–CF_3–$PhSe)_2$ in female mice, employing the forced swimming test. The involvement of the serotonergic and opioid systems in the antidepressant-like effect of (m–CF_3–$PhSe)_2$ was appraised. (m–CF_3–$PhSe)_2$ at doses of 50 and 100 mg/kg (p.o.) exhibited antidepressant-like action in the forced swimming test. The effect of (m–CF_3–$PhSe)_2$ (50 mg/kg p.o.) was prevented by pretreatment of mice with WAY100635 (0.1 mg/kg, s.c. a selective 5-HT_{1A} receptor antagonist), ritanserin (4 mg/kg, i.p., a non-selective $5HT_{2A/2C}$ receptor antagonist), ondansetron (1 mg/kg, i.p., a selective 5-HT_3 receptor antagonist) and naloxone (1 mg/kg, i.p., a non-selective antagonist of opioid receptors). These results suggest that (m–CF_3–$PhSe)_2$ produced an antidepressant-like effect in the mouse forced swimming test and this effect seems most likely to be mediated through an interaction with serotonergic and opioid systems.

1. Introduction

Depression is characterized by a wide range of debilitating emotional and physical symptoms. Numerous neural pathways are involved in the pathophysiology of depression. Therefore, a great number of monoamine neurotransmitters participate in the underlying mechanisms of antidepressants (Palucha and Pile, 2002). The causes of depression have been, in part, attributed to the dysregulation of one or all of these monoamine neurotransmitters at the synapse (Prange et al., 1974), principally the serotonin (5-HT) (Nutt, 2008), which plays important role in mediating behavioral effects of antidepressant drugs (Millan, 2004; Papakostas, 2006). Most of the prescribed antidepressants directly affect 5-HT turnover in the brain (Kreiss and Lucki, 1995), inhibit 5-HT reuptake and also interact with 5-HT_{1A} and 5-HT_2 receptors (Cryan et al., 2005).

Besides the well-known involvement of the monoaminergic system in the mechanism of action of classical antidepressants, substantial evidence supports the theory that the activation of the opioid system is implicated in the mechanisms underlying the effect of antidepressants (Devoize et al., 1984; Tejedor-Real et al., 1995; Zomkowski et al., 2005), although opioid compounds are mainly used for the treatment of pain. In this way, early studies showed that chronic administration of the opioid antagonist naltrexone induces a depression-like syndrome, indicating a general role for opioid system in depression (Hollister et al., 1981). Other studies have shown that patients with severe depression coupled with anxiety display decreased serum β-endorphin levels (Darko et al., 1992; Djurovic et al., 1999) and decreased μ-opioid receptor availability (Kennedy et al., 2006). Furthermore, some clinical reports describe the effectiveness of the μ-opiate agonists, oxycodone and oxymorphone, and the partial agonist, buprenorphine in patients with refractory major depression (Bodkin et al., 1995; Stoll and Rueter, 1999).

Selenium is an essential trace element nutritionally important to mammals, with physiological roles as a structural component of several antioxidant enzymes involved in the peroxide decomposition (Ursini and Bindoli, 1987; Rayman, 2000). It has been reported that insufficient selenium intake affects some psychological parameters and that selenium supplementation is associated with an improvement in mood and depression status (Benton and Cook, 1991; Benton, 2002).

m-Trifluoromethyl-diphenyl diselenide [(m–CF_3–$PhSe)_2$] is an organoselenium compound, which displays some pharmacological properties, such as antioxidant (Prigol et al., 2009a) and antipsychotic (Machado et al., 2006). Moreover, (m–CF_3–$PhSe)_2$ produces an anxiolytic effect (Brüning et al., 2009) which is related to the interaction with 5-HT receptors and selective inhibition of monoamine oxidase A (MAO-A), a key enzyme implicated in 5-HT

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doi:10.1016/j.ejphar.2011.02.039

metabolism. In addition, we recently showed that (*m*–CF_3–PhSe)$_2$ has antinociceptive action by interacting with μ and δ opioid receptors (Brüning et al., 2010).

In view of the above considerations, the antidepressant-like effect of (*m*–CF_3–PhSe)$_2$ was investigated in the mouse forced swimming test. The hypothesis that serotonergic and opioid systems are involved in the antidepressant-like action of (*m*–CF_3–PhSe)$_2$ in the forced swimming test was tested.

2. Materials and methods

2.1. Experimental animals

Behavioral experiments were conducted using Swiss female mice (25–35 g). Female mice were randomly selected without monitoring the estrous cycle (Duarte et al., 2007). Animals were maintained at 22–25 °C with free access to water and food, under a 12:12 hour light/dark cycle, with lights on at 7:00 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. Animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, of 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.

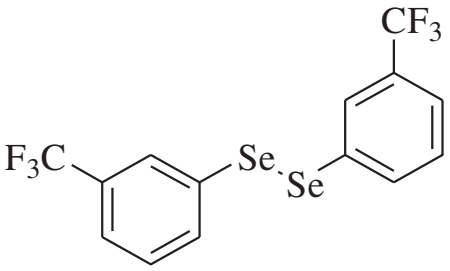
2.2. Drugs

(*m*–CF_3–PhSe)$_2$ (Fig. 1) was prepared and characterized in our laboratory by the method previously described (Paulmier, 1986). 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 (*m*–CF_3–PhSe)$_2$ (99.9%) was determined by GC/MS. N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-N-2pyridinylcyclohexanecarboxamide (WAY100635), naloxone hydrochloride and ritanserin were purchased from Sigma Chemical Co. (St Louis, Missouri, USA). All other chemicals were of analytical grade and obtained from standard commercial suppliers. All drugs were dissolved in saline, except (*m*–CF_3–PhSe)$_2$ that was dissolved in canola oil and ritanserin that was dissolved in saline with 1% of Tween 80. Mice received all drugs in a constant volume of 10 ml/kg body weight. Appropriate vehicle-treated groups were also assessed simultaneously. Pretreatment time of 30 min for administration of (*m*–CF_3–PhSe)$_2$ was based on previously published reports (Brüning et al., 2009; Prigol et al., 2009b).

2.3. Behavioral tests

2.3.1. Forced swimming test

The forced swimming test, as originally described by Porsolt et al. (1977a,b), is the most widely used model to screen new antidepressant drugs. This test is quite sensitive and relatively specific to all major classes of antidepressant drugs including tricyclics, serotonin-specific reuptake inhibitors, monoamine oxidase inhibitors, and atypical (Porsolt et al., 1977b; Cryan and Lucki, 2000; Cryan et al., 2002). All the mechanisms of action of treatments could be determined in the forced swimming test, but clinical correlations should be considered very carefully (Petit-Demouliere et al., 2005).



m-trifluoromethyl-diphenyl diselenide

Fig. 1. Chemical structure of *m*-trifluoromethyl-diphenyl diselenide (*m*–CF_3–PhSe)$_2$.

In this test, 30 min after the p.o. administration of (*m*–CF_3–PhSe)$_2$ (1–100 mg/kg) or canola oil (vehicle), mice were individually forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm), containing 19 cm of water at 25 ± 1 °C. The total duration of immobility was recorded during 6 min period. Each mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water. A decrease in the duration of immobility is indicative of an antidepressant-like effect (Porsolt et al., 1977a,b). Paroxetine (8 mg/kg, i.p., a selective serotonin reuptake inhibitor, SSRI) (Gay et al., 2010) and morphine (5 mg/kg, s.c., a nonselective opioid agonist) (Zomkowski et al., 2005), administered 45 and 30 min before the forced swimming test, respectively, were used as positive controls.

2.3.2. The role of the serotonergic system in the antidepressant-like effect of (*m*–CF_3–PhSe)$_2$ in the forced swimming test

To address the role of the serotonergic system in the antidepressant-like effect of (*m*–CF_3–PhSe)$_2$ on the forced swimming test, distinct groups of animals were treated with different classes of drugs. For this purpose, mice were pretreated with WAY100635, a selective 5-HT_{1A} receptor antagonist (0.1 mg/kg, s.c.) (Savegnago et al., 2007), ritanserin, a non-selective anatagonist of 5-$HT_{2A/2C}$ receptors (4 mg/kg, i.p.) (Wang et al., 2008) or ondansetron, a selective 5-HT_3 receptor antagonist (1 mg/kg, i.p.) (Savegnago et al., 2007). 15 min after WAY100635, ritanserin or ondansetron administration, (*m*–CF_3–PhSe)$_2$ (50 mg/kg, p.o.) or canola oil was administered, and 30 min later the forced swimming test was carried out.

2.3.3. The role of the opioid system in the antidepressant-like effect of (*m*–CF_3–PhSe)$_2$ in the forced swimming test

To investigate the possible contribution of the opioid system to the effect of (*m*–CF_3–PhSe)$_2$ on reducing the immobility time in the forced swimming test, animals were pretreated with naloxone (1 mg/kg, i.p., a non-selective antagonist of opioid receptors) (Kaster et al., 2007) or vehicle and after 30 min they received (*m*–CF_3–PhSe)$_2$ (50 mg/kg) or vehicle and were tested in the forced swimming test 30 min later.

2.3.4. Open-field test

The locomotor and exploratory behavior was assessed in the open-field test. The open-field was made of plywood and surrounded by walls 30 cm in height. The floor of the open-field, 45 cm in length and 45 cm in width, was divided by masking tape markers into 9 squares (3 rows of 3). Each animal was placed individually at the center of the apparatus and observed for 4 min to record the locomotor (number of segments crossed with the four paws) and exploratory activities (expressed by the number of time rearing on the hind limbs) (Walsh and Cummins, 1976). We have previously demonstrated that (*m*–CF_3–PhSe)$_2$ (0.1–100 mg/kg) has no effect on locomotor and exploratory behavior of mice in the open-field test (Brüning et al., 2009). In addition, the interaction of (*m*–CF_3–PhSe)$_2$ (100 mg/kg) with WAY100635 (0.1 mg/kg) (Brüning et al., 2009) or naloxone (1 mg/kg) (Brüning et al., 2010) did not cause any change in the locomotor activity assessed in the open-field test.

To verify whether the administration of (*m*–CF_3–PhSe)$_2$ with ritanserin or ondansetron impairs motor abilities mice were pretreated with ritanserin (4 mg/kg, i.p.) or ondansetron (1 mg/kg i.p.) and 15 min after (*m*–CF_3–PhSe)$_2$ (50 mg/kg, p.o.) or canola oil was administered. Thirty minutes later, the open-field test was carried out.