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Involvement of L-arginine–nitric oxide–cyclic guanosine monophosphate pathway in the antidepressant-like effect of bis selenide in the mouse tail suspension test

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ABSTRACT

The present study investigated a possible antidepressant-like effect of bis selenide by using the forced swimming and the tail suspension tests. The involvement of the L-arginine–nitric oxide–cyclic guanosine monophosphate signaling pathway in the antidepressant-like action of bis selenide was investigated. Bis selenide, given by oral route at doses of 0.5–5 mg/kg, decreased the immobility time in the forced swimming and tail suspension tests. Pretreatment with L-arginine (750 mg/kg, intraperitoneal, i.p., a nitric oxide precursor), sildenafil (5 mg/kg, i.p., a phosphodiesterase 5 inhibitor) or S-nitroso-N-acetyl-penicillamine (25 μg/site, intracerebroventricular, i.c.v., a nitric oxide donor) reversed the reduction in the immobility time elicited by bis selenide (1 mg/kg, p.o.) in the tail suspension test. Bis selenide (0.1 mg/kg, p.o., a subeffective dose) produced a synergistic antidepressant-like effect with N^G-nitro-L-arginine (0.3 mg/kg, i.p., an inhibitor of nitric oxide synthase) or 7-nitroindazole (25 mg/kg, i.p., a specific neuronal nitric oxide synthase inhibitor) in the tail suspension test. Pretreatment of animals with methylene blue (10 mg/kg, i.p., an inhibitor of nitric oxide synthase and soluble guanylate cyclase) or 1H-[1,2,4] oxadiazolo [4,3-a]quinoxalin-1-one (30 pmol, i.c.v., a specific inhibitor of soluble guanylate cyclase), at subeffective doses, caused a synergistic effect with bis selenide in the tail suspension test. Bis selenide (1 mg/kg, p.o.), at an effective dose in the forced swimming and tail suspension tests, caused a significant decrease in the mouse cerebral nitrate/nitrite levels. The antidepressant-like effect of bis selenide in the tail suspension test is dependent on the inhibition of the L-arginine–nitric oxide–cyclic guanosine monophosphate pathway.

1. Introduction

Depressive disorders represent a major public health problem due to their high prevalence and psychosocial impact. The World Health Organization (WHO) ranks unipolar depression as the fourth most important cause of mortality and disability (Murray and Lopez, 1997). Although underlying pathophysiological mechanisms of depression are not completely identified, novel targets have been identified for the development of new pharmacological and behavioural treatments (D'Aquila et al., 2000; Elhwuegi, 2004; Papakostas, 2006).

Numerous neural pathways are involved in the pathophysiology of depression. A great number of neurotransmitters participate in the underlying mechanisms of drugs (Palucha and Pilc, 2002). Nitric oxide donors and inhibitors have been shown to affect serotonin release in a dose-dependent manner in rodents (Lorrain and Hull, 1993; Kaehler et al., 1999). Studies have shown that the inhibition of nitric oxide synthase could be used as a strategy to enhance the clinical efficacy of serotonergic antidepressants (Smith and Whitton, 2000; Harkin et al., 2004). Further support for the hypothesis that the inhibition of nitric oxide synthase, with a subsequent decrease in the concentration of cyclic guanosine monophosphate (Snyder, 1992), may produce antidepressant-like effects, at least under certain conditions, comes from the reported reduction in the immobility time in the forced swimming test elicited either by the administration of methylene blue, which acts as a direct inhibitor of both nitric oxide synthase and soluble guanylate cyclase (Eroglu and Caglayan, 1997) or by the specific inhibitor of soluble guanylate cyclase activity, 1H-(1,2,4)-oxodiazolo (4,3-a)quinoxalin-1-one (Heiberg et al., 2002; Kaster et al., 2005; Ergün and Ergün, 2007).

Bis selenide has been reported to have pharmacological properties, such as antioxidant (Savegnago et al., 2006), antinociceptive and anti-inflammatory (Jesse et al., 2007, 2008a). There are also other organoselenium compounds (diphenyl diselenide and ebselen) whose therapeutic potential has been assessed in a variety of animal models such as the forced swimming and tail suspension tests (Savegnago et al., 2007, 2008; Posser et al., 2009). In addition, the inhibition of nitric oxide- cyclic guanosine monophosphate synthesis was previously shown to be involved in the diphenyl diselenide antidepressant-like effect (Savegnago et al., 2008).

In this way, it has been reported that low selenium status leads to depressed mood while high dietary and/or supplementary selenium improves mood. Moreover, several research groups have demonstrated that low selenium status has been associated with a significantly

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increased incidence of depression, anxiety, confusion, and hostility (Hawkes and Hornbostel, 1996; Rayman, 2000).

The primary aim of the present study was to investigate the antidepressant-like effect of bis selenide administered by per oral (p.o.) route to mice in the tail suspension and forced swimming tests, being that both tests used to screen new antidepressants (Cryan et al., 2002; Bourin et al., 2005). The second objective of this study was to investigate the involvement of the L-arginine–nitric oxide–cyclic guanosine monophosphate pathway in the antidepressant-like activity of bis selenide in the mouse tail suspension test. Finally, the current study was also performed to examine cerebral nitrate/nitrite levels in mice treated with bis selenide.

2. Materials and methods

2.1. Animals

The behavioural experiments were conducted using male adults 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] (Fig. 1) was prepared and characterized in our laboratory by the method previously described. For further details, refer to the following compound (2u) (Moro et al., 2005). The chemical purity of bis selenide (99.9%) was determined by gas chromatography/high-performance liquid chromatography. Chemo-physical properties: Yield: 0.285 g (65%). ^{1}H NMR, $CDCl_3$, 400 MHz, (ppm): 7.51–7.45 (m, 4H), 7.34 (s, 1H), 7.30–7.25 (m, 4H), 4.15 (d, *J*) (5.41 Hz, 2H), 1.83 (t, *J*) (6.28 Hz, 1H). ^{13}C NMR, $CDCl_3$, 100 MHz, (ppm): 134.5, 134.3, 133.9, 133.6, 133.4, 132.3, 129.5, 129.5, 128.2, 126.7, 67.5. MS (EI, 70 eV) *m/z* (relative intensity): 438 (10), 379 (17), 251 (62), 228 (52), 216 (100), 190 (77), 156 (58), 111 (38). HRMS: calcd for $C_{15}H_{12}C_{l2}OSe_2$ 437.8596, found 437.8601. The following drugs were used: L-arginine, methylene blue, S-nitroso-N-acetyl-penicillamine, sildenafil, (1H-[1,2,4] oxadiazolo[4,3-a]quinoxalin-1-one), N^G-nitro-L-arginine, 7-nitroindazole, VCl_3, N-(1-naphthyl) ethylene-diamine dihydrochloride, sulfanilamide and all other chemicals were purchased from Sigma Chemical USA.

2.3. Treatment

2.3.1. Antidepressant-like effect of bis selenide in the tail suspension and forced swimming tests

Time-course analysis of the antidepressant-like effect of bis selenide was performed. Mice were pretreated with bis selenide (5 mg/kg, p.o.) or with canola oil (10 ml/kg, p.o.) 0.5–8 h before the tail suspension test.

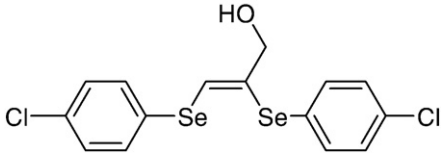

Fig. 1. Chemical structure of bis selenide (*Z*)-2, 3-bis(4-chlorophenylselanyl)prop-2-en-1-ol.

In order to assess the antidepressant-like effect of bis selenide, this compound was administered (dose range: 0.1–5 mg/kg, p.o.) 1 h before the forced swimming test, tail suspension test or open field test. We evaluated the locomotor activity in mice and immediately after the same mice were assessed in the forced swimming test or the tail suspension test.

2.3.2. Mechanisms involved in the antidepressant-like effect of bis selenide

The role played by the L-arginine–nitric oxide–cyclic guanosine monophosphate pathway in the antidepressant-like effect caused by bis selenide in the tail suspension test was investigated in distinct groups of animals. For this purpose, mice were pretreated with L-arginine, a precursor of nitric oxide (750 mg/kg, i.p., a dose that produces no effect in the tail suspension test), sildenafil, a specific type 5 phosphodiesterase inhibitor (5 mg/kg, i.p., a dose that produces no effect in the tail suspension test) or with the nitric oxide donor, S-nitroso-N-acetyl-penicillamine (25 μg/site, i.c.v., a nitric oxide donor, a dose that produces no effect in the tail suspension test). Thirty minutes after L-arginine, sildenafil or S-nitroso-N-acetyl-penicillamine, bis selenide (1 mg/kg, p.o., a dose effective in the tail suspension test) or vehicle was administered, and 1 h later the tail suspension test was carried out.

In another set of experiments, the synergistic effect of bis selenide (0.1 mg/kg, p.o., a subeffective dose) with a subeffective dose of N^G-nitro-L-arginine (0.3 mg/kg, i.p., an inhibitor of nitric oxide synthase), 7-nitroindazole (25 mg/kg, i.p., a specific neuronal nitric oxide synthase inhibitor), methylene blue (10 mg/kg, i.p., an inhibitor of nitric oxide synthase and soluble guanylate cyclase) or 1H-[1,2,4] oxadiazolo [4,3-a] quinoxalin-1-one (30 pmol/site, i.c.v., a specific soluble guanylate cyclase inhibitor) was investigated. Bis selenide (0.1 mg/kg, p.o.) or vehicle (p.o.) was administered 1 h before drugs. After 30 min of the i.p. administration of N^G-nitro-L-arginine, 7-nitroindazole, methylene blue or the i.c.v. injection of 1H-[1,2,4] oxadiazolo [4,3-a]quinoxalin-1-one the tail suspension test was carried out. The open field test was carried out to rule out any psychostimulant effect of the interaction of drugs and bis selenide.

2.3.3. Drug administration schedule

All drugs were dissolved in saline solution (0.9% NaCl), except 1H-[1,2,4] oxadiazolo [4,3-a]quinoxalin-1-one and 7-nitroindazole that were dissolved in 15% dimethyl sulfoxide and were made up to a final volume by the addition of 0.9% NaCl. Bis selenide was dissolved in canola oil. Mice received all drugs in a constant volume of 10 ml/kg body weight, except S-nitroso-N-acetyl-penicillamine and 1H-[1,2,4] oxadiazolo [4,3-a]quinoxalin-1-one which were injected by i.c.v. route (5 μl/site). Appropriate vehicle treated groups were also assessed simultaneously. Doses and the schedule of administration were chosen on the basis of experiments previously performed by our research group (Savegnago et al., 2008; Jesse et al., 2008b) and others (Almeida et al., 2006; Brocardo et al., 2008).

2.3.4. Intracerebroventricular injection technique

The i.c.v. administration was performed under light ether anesthesia. Briefly, a 0.4 mm external diameter hypodermic needle attached to a cannula, which was linked to a 25 μl Hamilton syringe, was inserted perpendicularly through the skull and no more than 2 mm into the brain of the mouse. A volume of 5 μl was then administered in the left lateral ventricle. The injection was given over 30 s, and the needle remained in place for another 30 s in order to avoid the reflux of the substances injected. The injection site was 1 mm to the right or left from the mid-point on a line drawn through to the anterior base of the ears (Kaster et al., 2005). To ascertain that the drugs were administered exactly into the cerebral ventricle, the brains were dissected and examined macroscopically after the test. Control animals received a saline injection by i.c.v. route in a similar manner.