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Antidepressant-like effect of the organoselenium compound ebselen in mice: Evidence for the involvement of the monoaminergic system

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ABSTRACT

Ebselen [2-phenyl-1,2-benzisoselenazol-3(2H)-one] is a seleno-organic compound which possesses a potent antioxidant activity and has been shown to exert neuroprotective effects *in vitro* and *in vivo* in a variety of pro-oxidative insults. The present study investigates a possible antidepressant activity of ebselen using two predictive tests for antidepressant activity in rodents: the forced swimming test and tail suspension test. Additionally, the mechanisms involved in the antidepressant-like effect of ebselen in mice were also assessed. Ebselen (10 mg/kg, s.c.) decreased the immobility time in the forced swimming test without accompanying changes in ambulation in the open-field test. In contrast, the administration of ebselen (10–30 mg/kg) did not produce any effect in the tail suspension test. The anti-immobility effect of ebselen (10 mg/kg, s.c.) was not prevented by pre-treatment of mice with *p*-chlorophenylalanine (PCPA, 100 mg/kg, i.p., an inhibitor of serotonin synthesis, 4 consecutive days), NAN-190 (0.5 mg/kg, i.p., a serotonin 5-HT_{1A} receptor antagonist) or ketanserin (5 mg/kg, i.p., a serotonin 5-$HT_{2A/2C}$ receptor antagonist). On the other hand, the pre-treatment 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), SCH23390 (0.05 mg/kg, s.c., a dopamine D_1 receptor antagonist) or sulpiride (50 mg/kg, i.p., a dopamine D_2 receptor antagonist) completely blocked the antidepressant-like effect of ebselen (10 mg/kg, s.c.) in the forced swimming test. It may be concluded that ebselen produces an antidepressant-like effect in the forced swimming test that seems to be dependent on its interaction with the noradrenergic and dopaminergic systems, but not with the serotonergic system.

1. Introduction

Depression is a chronic, recurring and potentially life-threatening illness that affect up to 20% of the population across the globe (Wong and Licinio, 2001; Nestler et al., 2002; Berton and Nestler, 2006). This disease is one of the top ten causes of morbidity and mortality worldwide and represents a high cost to countries economy (Wong and Licinio, 2001; Berton and Nestler, 2006). Available therapy for depression treatment is often associated with several undesirable side effects, and its effectiveness achieves only a certain portion of the population (Wong and Licinio, 2001; Richelson, 2001; Nestler et al., 2002; Berton and Nestler, 2006). Therefore, the identification of alternative therapeutic tools for the treatment of depression is of high importance.

Reactive oxygen species play an important role in the pathogenesis of many diseases, particularly in neurological and psychiatric disorders due to the actions of these species on cell function and the relatively high vulnerability of the central nervous system to oxidative stress (Bilici et al., 2001; Takuma et al., 2004; Eren et al., 2007). A series of studies performed in humans correlate depressive disorders with oxidative stress either in the brain and blood (Bilici et al., 2001; Sarandol et al., 2006; Michel et al., 2007). Moreover, a decrease in antioxidant enzyme activities in patients diagnosed with major depression has been demonstrated, while the antidepressant treatment ameliorated this effect (Herken et al., 2007). It has been well demonstrated that reactive oxygen species (ROS) modulate reversibly the synaptic transmission (Chen et al., 2001) as decreasing glutamate (Gilman et al., 1992; Zoccarato et al., 1995) and dopamine release (Joseph et al., 1996; Chen et al; 2001). Oxidation of catecholamines such as dopamine and norepinephrine by monoamine oxidase (MAO) may result in increased radical burden (Herken et al., 2007). Controlled studies pointed that MAO enzyme activity increases in patients with major depression (Pandey et al., 1992), suggesting an association between monoamine oxidation and overproduction of

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ROS in these patients (Herken et al., 2007). Thus, one might suppose that antioxidants could provide important protective effects against oxidative stress in psychiatric disorders as depression.

The seleno-organic compound ebselen (2-phenyl-1,2-benzisoselenazol-3(2H)-one, also called PZ51), (Fig. 1), was originally synthesized while searching for compounds that mimic the activity of the endogenous antioxidant glutathione peroxidase (Muller et al., 1984; Sies, 1993). This enzyme catalyzes the reduction of a wide variety of hidroperoxides (ROOH and H_2O_2) using GSH as a reductant, and constitutes a powerful cellular defense system against oxidative stress (Nogueira et al., 2004). Moreover, *in vitro* studies have shown that ebselen modulates the redox state of a wide spectrum of targets including receptors and proteins involved in neurotransmission (Jacob et al., 1998; Dimmeler et al., 1991; Schewe, 1995; Herin et al., 2001). Ebselen has been also shown to act as a neuroprotective agent in humans (Yamaguchi et al., 1998; Saito et al., 1998) and animals (Imai et al., 2003; Burger et al., 2005; Moretto et al., 2005; Xu et al., 2006). Regarding this aspect, a great amount of evidence has shown that several well-established antidepressant as well as putative antidepressant agents exhibit neuroprotective properties and regulate neuroplasticity and cell survival (Kolla et al., 2005; Brocardo et al., 2007; Huang et al., 2007; Peng et al., 2008; Tsai, 2007).

In spite of the large number of evidence that indicates ebselen as a promising pharmacological agent possessing antioxidant and neuroprotective activities, investigations regarding the potential neurobehavioral properties of ebselen are absent. Herein, the antidepressant-like action of ebselen was tested in the forced swimming test and the tail suspension test. Both tests are behavioral models widely used for screening compounds or drugs with antidepressant-like effects and are important tools to study neurobiological mechanisms involved in antidepressant responses (Barauna et al., 2006; Machado et al., 2007; Kaster et al., 2007).

2. Materials and methods

2.1. Animals

Adults male Swiss mice (30–40 g) were maintained at 22–27 °C with free access to water and food, under a 12:12 h light:dark cycle (lights on at 7:00 h). Twenty mice were housed per cage. The cages were placed in the experimental room 24 h before the test for acclimatization. All manipulations were carried out between 9:00 and 17:00 h, with each animal used only once. All procedures in this study were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the local Ethics Committee. All efforts were made to minimize animal suffering and the number of animals used in the experiments.

2.2. Drugs and treatment

The following drugs were used: ketanserin tartarate, 1-(2-methoxyphenyl)-4[-(2-phthalimido)butyl]piperazine) (NAN-190), p-chlorophenylalanine methyl ester (PCPA), sulpiride, prazosin, yohimbine, (*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH23390), fluoxetine (all from Sigma Chemical Company, St. Louis, MO, U.S.A.). Ebselen [2-phenyl-1,2-benzisoselenazol-3(2H)-one] (Fig. 1) was synthesized according to Engman (1989). Analysis of the ^{1}HNMP and ^{13}CNMR spectra showed that the compound presented analytical and spectroscopic data in full agreement with its assigned structure.

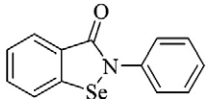

Fig. 1. Chemical structure of ebselen.

All drugs were administered by intraperitoneal (i.p.) route in a constant volume of 10 ml/kg body weight, except ebselen and SCH 23390 that were administered by subcutaneous (s.c.) route (10 ml/kg body weight). Drugs were dissolved in saline, except ebselen that was diluted in mineral oil, NAN-190 that was diluted in saline containing 1% Tween 80 and sulpiride that was diluted in saline containing 5% DMSO. Control animals received appropriate vehicle.

In order to investigate the possible antidepressant-like effect of ebselen, animals received s.c. administration of ebselen (dose range 3–30 mg/kg) 30 min before the forced swimming test, tail suspension test or open-field test. In the experiments designed to study the time-course effect of ebselen (10 mg/kg), the immobility time in the forced swimming test was assessed in an independent group of mice, 30, 60, 120 and 240 min after the administration of ebselen (10 mg/kg).

To test the involvement of the serotonergic system in the antidepressant-like effect of ebselen, mice were pretreated with PCPA (100 mg/kg, an inhibitor of serotonin synthesis) or vehicle, once a day, for 4 consecutive days (Rodrigues et al., 2002; Kaster et al., 2005). Then, 24 h after the last PCPA or vehicle injection, animals were treated with ebselen (10 mg/kg, s.c.), fluoxetine (32 mg/kg, i.p., a positive control) or vehicle and were tested in the forced swimming test 30 min later.

In a separate series of experiments, we also investigated the involvement of the serotonin (5-HT) receptor subtypes in the effect of ebselen in the forced swimming test. For this purpose, mice were pretreated with NAN-190 (0.5 mg/kg, a serotonin 5-HT_{1A} receptor antagonist), ketanserin (5 mg/kg, a preferential serotonin 5-HT_{2A} receptor antagonist) or vehicle and after 30 min they received ebselen (10 mg/kg) or vehicle injection before being tested in the forced swimming test 30 min later.

To assess the possible involvement of the noradrenergic and the dopaminergic systems in the antidepressant-like effect of ebselen in the forced swimming test, animals were pretreated with prazosin (1 mg/kg, i.p., an α_1-adrenoceptor antagonist), yohimbine (1 mg/kg, i.p., an α_2-adrenoceptor antagonist), SCH23390 (0.05 mg/kg, s.c., a dopamine D_1 receptor antagonist) or sulpiride (50 mg/kg, i.p., a dopamine D_2 receptor antagonist), and after 30 min they received ebselen (10 mg/kg, s.c.) or vehicle and were tested in the forced swimming test 30 min later.

Doses and drugs administration schedule were all based in previous studies (Redrobe and Bourin, 1997; O'Neill and Conway, 2001; Rodrigues et al., 2002; Yamada et al., 2004; Kaster et al., 2005, 2007) and it is noteworthy that drugs per se did not change the behavioral parameters.

2.3. Forced swimming test

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. 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., 1977).

2.4. Tail suspension test

The total duration of immobility induced by tail suspension was measured according to the method described by Steru et al. (1985). Briefly, mice both acoustically and visually isolated were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm

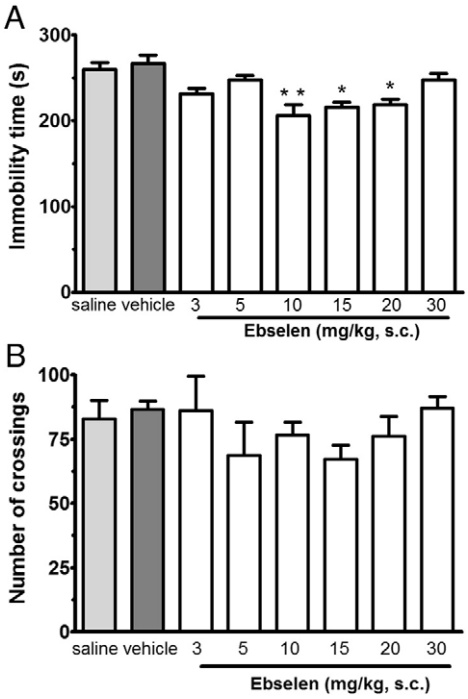

Fig. 2. Effect of ebselen administration (3–30 mg/kg, s.c.) in the forced swimming test (panel A), or in the open-field test (panel B). Ebselen was administered 30 min before the tests. Values are mean+S.E.M. (n=7–9). *P<0.05, **P<0.01 compared with the vehicle-treated control. (A) treatment [F(7,42)=6.12, p<0,01]; (B) treatment [F(7,28)=0.927, p=0.50].

from the tip of the tail. Immobility time was recorded during a 6-min period (Rodrigues et al., 2002; Machado et al., 2007).

2.5. Open-field test

The ambulatory behavior was assessed in an open-field test as described previously (Rodrigues et al., 1996). The apparatus consisted of a wooden box measuring 40×60×50 cm. The floor of the arena was divided into 12 equal squares. The number of squares crossed with all paws (crossing) was counted in a 6-min session.

2.6. Statistical analysis

All experimental results are given as the mean±S.E.M. Statistical analysis was performed by two-way ANOVA except in the studies of dose-response and time-course effect of ebselen that one-way ANOVA was performed. In all cases, Newman–Keuls test was applied for post-hoc comparison when appropriate. A value of P<0.05 was considered to be significant.

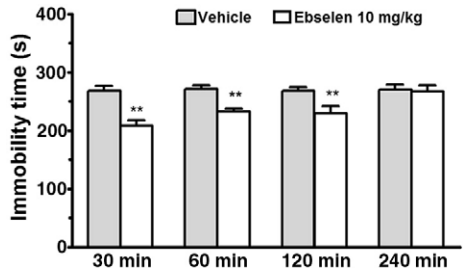

Fig. 3. Time-course effect of ebselen in the forced swimming test. Ebselen (10 mg/kg, s.c.) was administered 30, 60, 120 and 240 min before the forced swimming test. Values are expressed as mean+S.E.M., (n=5–6). **P<0.01 compared with the vehicle-treated group.

3. Results

3.1. Antidepressant-like effect of ebselen

The results depicted in Fig. 2A show the effect of the administration of ebselen (10–30 mg/kg) in the forced swimming test. Ebselen caused a statistically significant decrease in immobility time in the forced swimming test in mice at dose range 10–20 mg/kg. This effect was not observed at a higher dose of ebselen (30 mg/kg). When tested in the tail suspension test, ebselen (3–30 mg/kg) produced no effect in the immobility time (data not show). The administration of ebselen (3–30 mg/kg, i.p.) did not produce significant changes in ambulation of mice in the open-field arena as showed in Fig. 2B. Since 10 mg/kg was the lowest effective dose, all the next experiments were performed using this dose.

Fig. 3 shows a time-course analysis for the effect of ebselen (10 mg/kg) in the forced swimming test. The animals were tested in the forced

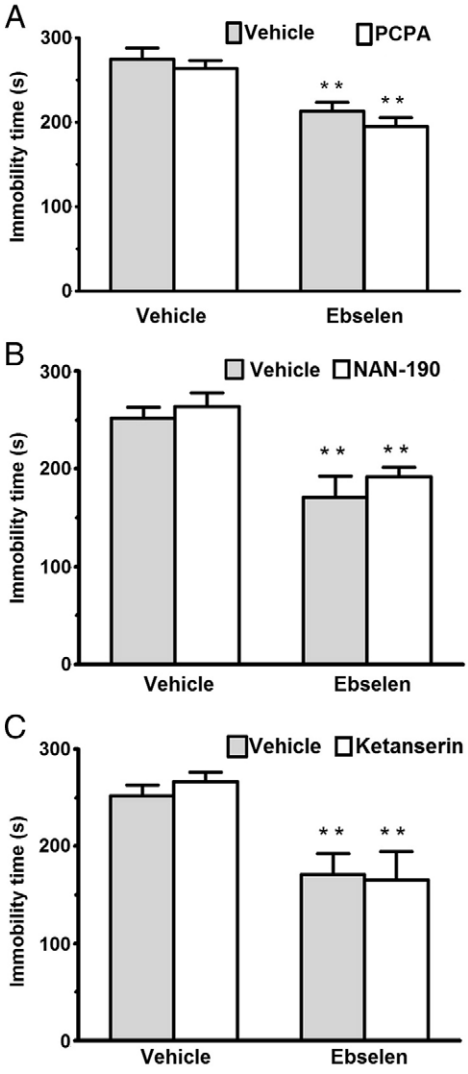

Fig. 4. Effect of pretreatment of mice with PCPA (100 mg/kg, i.p. once a day for 4 consecutive days, panel A), NAN-190 (0.5 mg/kg, i.p., panel B), ketanserin (5 mg/kg, i.p., panel C) on the ebselen (10 mg/kg, s.c.)-induced reduction in immobility time in the forced swimming test. Values are expressed as mean+S.E.M., (n=5–8). **P<0.01 compared with the vehicle-treated control. (A) Pretreatment [F(1,40)=1.47, p=0,23]; treatment [F(2,40)=16.47, p<0.01]; pretreatment×treatment interaction [F(2,40)=6.10, p<0.01]. (B) Pretreatment [F(1,19)=1.24, p=0.27]; treatment [F(1,19)=28.50, p<0.01]; pretreatment×treatment interaction [F(1,19)=0.10, p=0.75]. (C) Pretreatment [F(1,19)=0.04, p=0.83]; treatment [F(1,19)=20.54, p<0.01]; pretreatment×treatment interaction [F(1,19)=0.25, p=0,61].

swimming test 30, 60, 120 and 240 min after the administration of ebselen in independent groups. Ebselen produced a marked effect in the forced swimming test as early as 30 min after s.c. administration, an action that remained statistically significant until 120 min after drug administration.

3.2. Investigation of possible mechanisms underlying the antidepressant-like effect of ebselen in the forced swimming test

3.2.1. Involvement of the serotonergic system

Fig. 4A shows that the pretreatment of mice with the inhibitor of 5-HT synthesis PCPA (100 mg/kg, i.p., once a day by 4 consecutive days) did not affect the antidepressant-like effect of ebselen (10 mg/kg), but completely blocked the decrease in the immobility time elicited by fluoxetine, that was used as a positive control (32 mg/kg, i.p., data not shown). Moreover, the pretreatment of mice with antagonists of serotonin $5HT_{1A}$ and $5HT_{2A}$ receptors, NAN-190 (0.5 mg/kg, i.p.) or ketanserin (5 mg/kg, i.p.) respectively, was not able to reverse the anti-immobility effect of ebselen in the forced swimming test (Fig. 4B and C, respectively).

3.2.2. Involvement of the noradrenergic system

The results depicted in Fig. 5A and B show that pretreatment of mice with the α_1-adrenoceptor antagonist prazosin (1 mg/kg, i.p) and the α_2-adrenoceptor antagonist yohimbine (1 mg/kg, i.p.) was able to reverse ($P<0.01$) the antidepressant-like effect of ebselen (10 mg/kg) in the forced swimming test.

3.2.3. Involvement of the dopaminergic system

The anti-immobility effect of ebselen (10 mg/kg) was also significantly ($P<0.01$) prevented by pretreatment of mice with

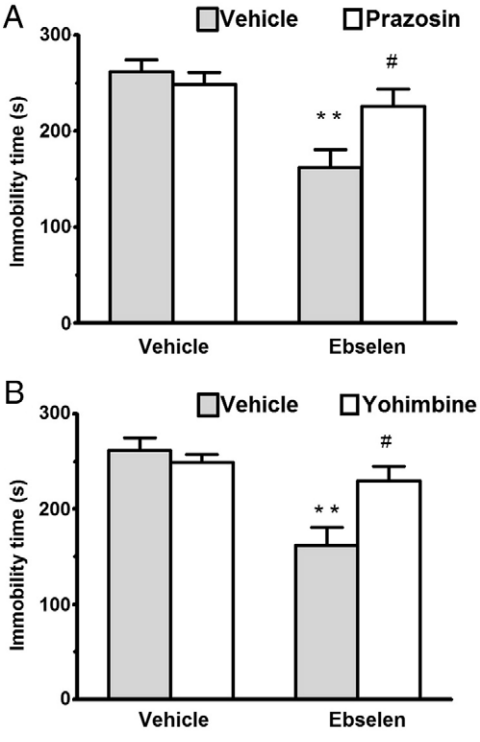

Fig. 5. Effect of pretreatment of animals with prazosin (1 mg/kg, i.p., panel A) or yohimbine (1 mg/kg, i.p., panel B), on ebselen (10 mg/kg, s.c.)-induced reduction in immobility time in the forced swimming test in mice. Values are expressed as mean+S.E.M. ($n=5–7$). $^{**}P<0.01$ compared with the control group; $^{\#}P<0.01$ when comparing with the same group pretreated with vehicle. (A) Pretreatment [$F(1,20)=3.11$, $p=0.09$]; treatment [$F(1,20)=15.06$, $p<0.01$]; pretreatment×treatment interaction [$F(1,20)=6.73$, $p<0.05$]. (B) Pretreatment [$F(1,21)=2.58$, $p=0.08$]; treatment [$F(1.21)=14.98$ $p<0.01$]; pretreatment×treatment interaction [$F(1.21)=5.82$, $p<0.05$.

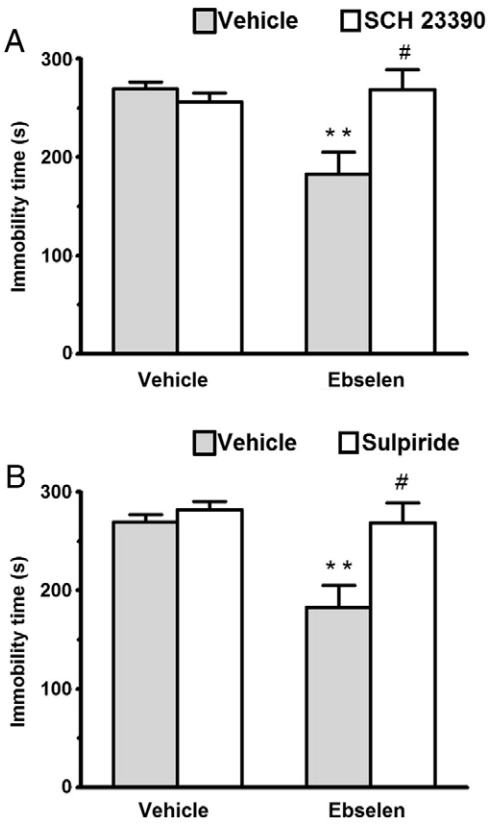

Fig. 6. Effect of pretreatment of mice with SCH23390 (0.05 mg/kg, s.c., panel A) or with sulpiride (50 mg/kg, i.p., panel B) on ebselen (10 mg/kg, s.c.)-induced reduction in immobility time in the forced swimming test. Values are expressed as mean+S.E.M. ($n=5–6$). $^{**}P<0.01$ compared with the control group; $^{\#}P<0.01$ when comparing with the same group pretreated with vehicle. (A) Pretreatment [$F(1,19)=9.98$, $p<0.01$]; treatment [$F(1,19)=4.97$, $p<0.05$]; pretreatment×treatment interaction [$F(1,79)=16.99$, $p<0.01$]. (B) Pretreatment [$F(1,19)=8.66$, $p<0.01$]; treatment [$F(1,19)=8.84$, $p<0.01$]; pretreatment×treatment interaction [$F(1,19)=4.88$, $p<0.05$.

SCH23390 (0.05 mg/kg, s.c.), a dopamine D_1 receptor antagonist and sulpiride (50 mg/kg, i.p.), a dopamine D_2 receptor antagonist (Fig. 6A and B, respectively).

4. Discussion

The biological properties of ebselen as an antioxidant, anti-inflammatory, antiatherosclerotic and neuroprotectant agent have been well described in animals (Schewe, 1995; Ozaki et al., 1997; Porciuncula et al., 2001; Farina et al., 2003; Moretto et al., 2004; Burger et al., 2005; Moretto et al., 2005; Xu et al., 2006) and in humans (Yamaguchi et al., 1998; Saito et al., 1998).

Our study shows that ebselen decreases the immobility time in the forced swimming test at a dose of 10 mg/kg which is consistent with an antidepressant-like action (Porsolt et al., 1977; Petit-Demouliere et al., 2005). This effect was observed at time points ranging from 30 min to 120 min after the injection. On the other hand, administration of this compound was not able to alter the immobility time of the mice in the tail suspension test. The forced swimming test and tail suspension test are widely used behavioral tools for screening antidepressant activity of different classes of drugs (Porsolt et al., 1977; Cryan et al., 2002; Petit-Demouliere et al., 2005; Cryan et al., 2005). These tests are based on the observation that rodents, after initial escape-oriented movements, develop an immobile posture when placed in an inescapable stressful situation. If antidepressant treatments are given prior to the test, the subjects will actively persist engaging in escape-directed behavior for longer periods of time than after vehicle treatment (Cryan et al., 2005). Differences in sensitivity

for each test are documented in a dependence of the drug tested (Porsolt and Lenegre, 1992; Cryan et al., 2005); as example rolipram and levoprotiline cause reduction of immobility in the forced swimming test but not in the tail suspension test (Porsolt and Lenegre, 1992). Furthermore, the modulation of serotonergic, noradrenergic and dopaminergic systems, among others, has been shown to be involved in the behavioral effects of antidepressants in these animal models (Cryan et al., 2002; Cryan et al., 2005; O'Leary et al., 2007). The reduction in the immobility time in the forced swimming test elicited by ebselen was not accompanied by changes in the locomotor activity assessed in the open-field test (Fig. 2C), which means that the effect of ebselen observed in forced swimming test cannot be attributable to a psychostimulant effect.

Depression has been associated with an impairment of serotonergic, noradrenergic and dopaminergic neurotransmission (Urani et al., 2005). Furthermore, the monoaminergic system is considered one of the main targets in the pathophysiology and treatment of depression (Elhwuegi, 2004; Millan, 2004). In this study we investigated the possible involvement of monoaminergic system in the antidepressant-like effect of ebselen. For this aim, we investigated the effects of several pharmacological antagonists/modulators of the monoaminergic system on the anti-immobility action of ebselen (10 mg/kg, s.c., 30 min before test) in mice.

Pharmacologic and genetic studies have demonstrated that serotonergic system plays a central role in the pathophysiology and etiology of depression (Ansorge et al., 2007) and this system plays a major role in the action of antidepressants (Millan, 2004). In spite the well demonstrated participation of serotonergic system in antidepressant mechanism, the involvement of this system in the antidepressant-like effect of ebselen was not observed. As indicated by the results, the effect of ebselen in forced swimming test was not reversed by pretreatment of mice with the neuronal 5-HT store depletor, PCPA, as well as with the serotonin 5-HT_{1A} and 5-HT_{2A} antagonists, NAN-190 and ketanserin, respectively.

PCPA is an inhibitor of tryptophan hydroxylase and its administration by four consecutive days depletes the endogenous stores of 5-HT by about 60% in mice while noradrenaline and dopamine levels are not affected (Redrobe et al., 1998). PCPA was reported to block the antidepressant-like effect of selective 5-HT reuptake inhibitors (SSRIs; i.e. fluoxetine, citalopram) in the tail suspension test and forced swimming test but not noradrenaline reuptake inhibitors (NRIs; i.e. reboxetine) or tricyclics (i.e. desipramine) (Page et al., 1999; O'Leary et al., 2007), consistent with the hypothesis that SSRIs compounds elicit their acute behavioral effects by increasing extracellular 5-HT (Bymaster et al., 2002). In our study the reduction on brain 5-HT by administration of PCPA did not prevent the antidepressant-like effect of ebselen, but prevented the antidepressant-like effect of fluoxetine. This result clearly indicates that, opposed to fluoxetine, the mechanism underlying the anti-immobility effect of ebselen in the forced swimming test is not dependent on the increase in 5-HT levels in the synaptic cleft. The absence of the involvement of serotonergic system in the mechanism of action of ebselen in the forced swimming test is reinforced by the demonstration that serotonin 5-HT_{1A} and 5-HT_{2A} receptors are not involved in the mechanism of action of ebselen, despite the well established role of these classes of receptors in the action of various antidepressant compounds (Middlemiss et al., 2002).

The role of noradrenaline in the pathophysiology of depression has been extensively investigated, since some antidepressant drugs increase the synaptic concentration of noradrenaline and they might act directly at noradrenergic receptors (Elhwuegi, 2004). In addition, it was demonstrated that noradrenaline-deficient mice lack responses to antidepressant drugs, including SSRIs (Cryan et al., 2004). In our study both prazosin (α_1-adrenoceptor antagonist) and yohimbine (α_2-adrenoceptor antagonist) were able to reverse the antidepressant-like effect of ebselen. This result indicates that the compound ebselen may exert its effect in the forced swimming test by interacting with both α_1 and α_2-adrenoceptors. Accordingly, there is compelling evidence for the role of α_1 and α_2- adrenoceptors in the mechanism of action of antidepressant agents as desipramine and amitriptyline (Kitada et al., 1983; Danysz et al., 1986; Millan, 2004).

The dopaminergic system is strongly implicated in the regulation of mood (Dailly et al., 2004). There is evidence deriving from clinical studies showing a decrease of plasma dopamine metabolites (homovanillic acid and 3,4-dihydroxyphenylacetic acid) in depressed patients, suggesting a diminished dopamine turnover in depression (Mitani et al., 2006; Sher et al., 2006). Moreover, it was demonstrated that chronic treatments with tricyclic antidepressants potentiated the dopaminergic neurotransmission, which may contribute to therapeutic effect of these drugs (Chiodo and Antelman, 1980; Serra et al., 1990; D'Aquila et al., 2000; Papakostas, 2006). Concerning the forced swimming test, the involvement of dopamine D1 and D2 receptors in the mechanism of action of various antidepressant drugs such as SSRIs as well as imipramine (a tricyclic antidepressant) and bupropion (an atypical antidepressant) (Dziedzicka-Wasylewska et al., 2000; Renard et al., 2001; Yamada et al., 2004) has been shown. In the present work we observed that both the selective dopamine D1 receptor antagonist SCH 23390 and the dopamine D2 receptor antagonist, sulpiride significantly antagonized the anti-immobility effects of ebselen in the forced swimming test. Indeed, our results point a participation of both dopamine D1 and D2 receptors in the antidepressant-like effects of ebselen.

Recently, diphenyl diselenide, another seleno-organic compound, was reported to produce antidepressant-like effect in forced swimming test in rats. However, differently from our findings with ebselen, the effect of diphenyl diselenide seems to involve both serotonergic and cathecolaminergic systems (Savegnago et al., 2007). Regardless of the fact that both compounds display similar antioxidant mechanism (Nogueira et al., 2004), the pharmacological targets underlying the behavioral effects of these compounds in the forced swimming test are different.

Ebselen has been reported as a neuroprotective agent both *in vitro* and *in vivo* (Porciuncula et al., 2001; Kalayci et al., 2005; Xu et al., 2006). In the present work we add new data indicating an antidepressant-like effect of ebselen after acute subcutaneous administration. This action is not related to psychostimulant effect and seems to be mediated by an interaction with the noradrenergic and dopaminergic systems, but not with the serotonergic system. Finally, our results raise perspectives for investigation of neurochemical mechanisms involved in antidepressant-like effect of ebselen as well as its potential use as a therapeutic agent in mood disorders.

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