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Ebselen attenuates haloperidol-induced orofacial dyskinesia and oxidative stress in rat brain

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Abstract

Haloperidol-induced orofacial dyskinesia is an animal model of tardive dyskinesia whose pathophysiology has been related to basal ganglia oxidative stress. In this study the authors examined whether ebselen, an antioxidant organochalcogen with glutatione peroxidase-like activity, changes the behavioral and neurochemical effect of sub-chronic haloperidol administration. Haloperidol administered (12 mg/kg/week, sc) for 4 weeks caused a significant increase in vacuous chewing movements (VCMs), tongue protrusion (TP) and the duration of facial twitching (FT) observed in 4 weekly evaluations ($p<0.05$). Ebselen (30 mg/kg, ip), administered every other day, along with haloperidol (12 mg/kg/week, sc) once weekly, reversed the increase of VCMs and FT in four weekly evaluations ($p<0.05$), while TP frequency was reverted in the 2nd, 3rd, and 4th week. After the treatments and behavioral observation, biochemical parameters in segments of the brain were analyzed. Haloperidol significantly increased the thiobarbituric acid-reactive species (TBARS) levels in the cortex, striatum and subcortical parts of the brain. The co-administration of ebselen reversed the effect of haloperidol on TBARS production in cortex and striatum. The results of the present study clearly indicate that ebselen has a protective role against haloperidol-induced orofacial dyskinesia and reverses the increase in TBARS production caused by haloperidol administration. Consequently, the use of ebselen as a therapeutic agent for the treatment of tardive dyskinesia should be considered.

Keywords: Ebselen; Haloperidol; Orofacial dyskinesia; Tardive dyskinesia; TBARS

1. Introduction

Tardive dyskinesia (TD) is defined as a motor disorder of the orofacial region resulting from chronic neuroleptic treatment that is characterized by repetitive involuntary movements, involving the mouth, face, tongue and sometimes limb and trunk musculature. TD appears months or years after the initiation of antipsychotic treatment, persists after drug withdrawal and may be irreversible (Andreassen and Jorgensen, 1994). The irreversibility of TD has been considered a major clinical issue in psychiatry and occurs in aproximately 20% of antipsychotic-treated patients (Lohr et al., 2003a,b). The precise pathophysiological basis of TD is not well understood, but the disorder has been associated with the use of typical or classical antipsychotic drugs such as haloperidol (Jackson-Lewis et al., 1991). Although there are new classes of atypical antipsychotic agents with lower incidence and risk of TD, the problem remains constant in clinical psychiatry (Llorca et al., 2002). Consequently, studies desirable that intend to explain the neuropathophysiology of TD are still needed.

The molecular mechanisms responsible for the neuropathophysiology of tardive dyskinesia are not completely understood. It has been suggested that the increase in the density of striatal dopaminergic D2 receptors observed in humans and in experimental rodent models of tardive dyskinesia coincides with the appearance of extrapyramidal side effects. In line with this, antidopaminergic drugs tend to suppress the behavioral manifestations of tardive diskynesia, whereas dopaminergic agonists exacerbate the syndrome (Baldessarini and Tarazi, 2001). Although D2

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receptor upregulation can play a role in TD, the dopaminergic hypothesis as the main molecular mechanism of TD has been questioned on several grounds (Klawans and Rubovits, 1972; Waddington, 1990; Wolfarth and Ossowska, 1989).

The participation of free-radicals derived from the metabolism of dopamine and/or from an enhancement of the glutamatergic transmission, secundary to presynaptic dopamine receptors blockadge has gained experimental support in the literature (Casey, 1995; Coyle and Puttfarcken, 1993; Lohr, 1991; Meshul et al., 1996; Naidu and Kulkarni, 2001; Tsai et al., 1998). In accordance, animal studies have demonstrated an enhancement to glutamatergic participation in the ethiology of TD in the behavioral response to NMDA in haloperidol-treated animals (Grimm et al., 1998).

In line with free radical hypothesis of TD, some clinical studies have reported beneficial effects of vitamin E on tardive dyskinesia (Dabiri et al., 1994; Egan et al., 1992; Elkashef et al., 1990; Shamir et al., 2001), but others found no effect (review by Barak et al., 1998). Further, the levels of lipid peroxidation products in the blood and cerebrospinal fluid of TD patients are increased, when compared to normal patients (Lohr et al., 2003a). Similarly, in animal models of tardive dyskinesia, different experimental paradigms have confirmed the protective action of antioxidants (Abilio et al., 2003a,b, 2002; Burger et al., 2003; Jackson-Lewis et al., 1991; Naidu et al., 2003; Raghavendra et al., 2001; Singh et al., 2003; Takeuchi et al., 1998), whereas pro-oxidants, such as aging and the mitochondrial neurotoxin 3-nitropropionic acid, aggravate reserpine- or haloperidol-induced orofacial dyskinesia (Bergamo et al., 1997; Calvente et al., 2002; Takeuchi et al., 1998; Burger et al. 2004).

Recently, ebselen, a lipid soluble seleno-organic compound with antioxidant activity (Sies, 1993; Parnham and Sies, 2000; Nogueira et al., 2004), has been show to have a protective role against reserpine-induced orofacial dyskinesia (Burger et al., 2003). Ebselen is also effective as a neuroprotecting agent against brain ischemia and stroke in humans and animal models (Dawson et al., 1995; Saito et al., 1998; Takasago et al., 1997; Tamaguchi et al., 1998; Yamaguchi et al., 1998) and in a variety of in vitro and in vivo models of neurotoxicity in rats (Imai et al., 2001; Moussaoui et al., 2000; Namura et al., 2001; Porciúncula et al., 2001; Rossato et al., 2002a,b). Considering the importance of studying the mechanism involved in TD pathogenesis and the necessity of searching for new compounds with potential usefulness in the treatment or prevention of TD, the authors examined the possible protective effect of ebselen on haloperidol-induced orofacial dyskinesia. In addition, since tardive dyskinesia can be caused by free radical overproduction in the brain, the effects of haloperidol and ebselen on lipid lipoperoxidation were examined by measuring thiobarbituric acid reactive species (TBARS) in the cortex, striatum and subcortical parts of the brain.

2. Method

2.1. Drugs

Haloperidol (haloperidol decanoate-Cristália, Brasil) was dissolved in Tween (a final concentration of 1%). Ebselen (2-phenyl-1,2 benzisoselenazol-3 (2H-one) was synthesized according to Engman (1989), dissolved in Tween (final concentration of 1%). The haloperidol solution or Tween 1% were injected subcutaneously (sc, once a week) and the ebselen solution or Tween 1% were injected intraperitoneally (ip, starting 5 days before haloperidol for a total of 33 days on alternate days. This resulted in a total of 16 injections of ebselen). All the solutions were injected in the volume of 1.0 mL/kg body weight.

2.2. Animals

Male Wistar rats weighing 270–320 g (about three-months of age) were used. Groups of 3–4 animals were kept in Plexiglas cages with free access to food and water in a room with controlled temperature (22 °C ± 3) and in a 12-h light/dark cycle with lights on at 7:00 am. The animals were maintained and used in accordance to the guidelines of the Committee on Care and Use of Experimental Animal Resources, School of Veterinary Medicine and Animal Science of the University of São Paulo, Brazil.

2.3. Experimental procedure

Subchronic haloperidol-induced orofacial dyskinesia- Twenty-eight rats were allocated randomly to four groups of seven animals each. The Control group (V) was injected with 1% Tween solution (ip) every other day and (sc) once a week. The group ebselen (E) received 30 mg/kg (ip) of ebselen solution every other day (ip) and 1% Tween solution (sc) once a week. Injection of ebselen (or vehicle) started 5 days before haloperidol injection. So, the rats received 2 injections of ebselen before haloperidol and 14 injections during haloperidol treatment. The haloperidol group (H) was injected with 1% Tween solution (ip) every other day and 12 mg/kg of haloperidol decanoate solution (sc) once a week (equivalent of 1.2 mg/kg/ per day of unconjugated haloperidol). The ebselen/haloperidol group (E+H) was injected with 30 mg/kg of ebselen solution (ip) every other day plus 12 mg/kg of haloperidol decanoate solution (sc) once a week. The administration of ebselen or Tween 1% (ip) preceded the haloperidol or vehicle (sc) solution by 30 min when the administrations occured on the same day. The lengh of complete haloperidol treatment was 28 days and haloperidol treated animals received a total of four subcutaneous injections of haloperidol solution or vehicle. All the animals were observed for the quantification of orofacial dyskinesia just before haloperidol administration on the 7th, 14th, 21st and 28th day after the first administration of haloperidol (or vehicle).

2.4. Behavioral testing

Rats were placed individually in cages (20 × 20 × 19 cm) containing mirrors under the floor and behind the back wall of the cage to allow behavioral quantification when the animal was faced away from the observer. To quantify the occurrence of oral dyskinesia, the incidence of tongue protusions (TP), vacuous chewing movements frequency (VCM), and the duration of facial twitching (FT) were recorded for 15 min. Observers were blind to the drug treatment. In a preliminary study (using 5 control and 10 rats treated with haloperidol) of interrater reability, we found that the use of this method of observation and definition for the parameters evaluated usually results in >97, 92, and 94% agreement between the 3 different observers for VCM, TP and duration of FT, respectively. All the calculated α values were significant for $p<0.05$.

2.5. Thiobarbituric reactive substances (TBARS) quantification

Rats were killed about 1 h after the last session of behavioral quantification (on 28th day after the first administration of haloperidol or vehicle). The brains were immediately excised and the cerebellum discarded. Brains were put on ice and the cortex, striatum and subcortical parts were separated, weighed and homogenized in 10 volumes (w/v) of 10 mM Tris–HCl, pH 7.5. The subcortical region of the brain comprised all the remaining parts of the forebrain after the dissection of the cerebral cortex and striatum, including hippocampus, thalamus, hypothalamus, amygdala and other subthalamic structures. The homogenates were centrifuged for 5 min at 1,500 × g and the supernatant was used for TBARS determination as described earlier (Ohkawa et al., 2004; Rossato et al., 2002a).

2.6. Statistical analysis

Data were analyzed by a three-way ANOVA, followed, when appropriate by univariate analysis and Duncan's Post Hoc test. For behavioral data, 2 (control/ebselen) × 2 (control/haloperidol) × 4 behavioral quantifications were performed, considering the last factor as a repeated measure. TBARS data were analysed by 2 (control/ebselen) × (control/haloperidol) × 3 brain regions, and brain regions were considered as a within-subject factor.

3. Results

Haloperidol (12 mg/kg/week) treatment for 28 days caused signs of orofacial dyskinesia that were apparent from day 7 onward, where tongue protusion (Fig. 1), vacuous chewing (Fig. 2) and facial twitching (Fig. 3) showed significant differences from the control group during the four weekly observations (all P values less than 0.05). Co-administration of ebselen (30 mg/kg) and haloperidol reduced the frequency of the haloperidol-induced VCMs (Fig. 2) and FT (Fig. 3) during all the behavioral sessions ($p<0.05$). Protection caused by ebselen of TP was evident from the second week onward in relation to the haloperidol group (Fig. 1). Treatment with ebselen alone caused only an isolated elevation in VCM in the first

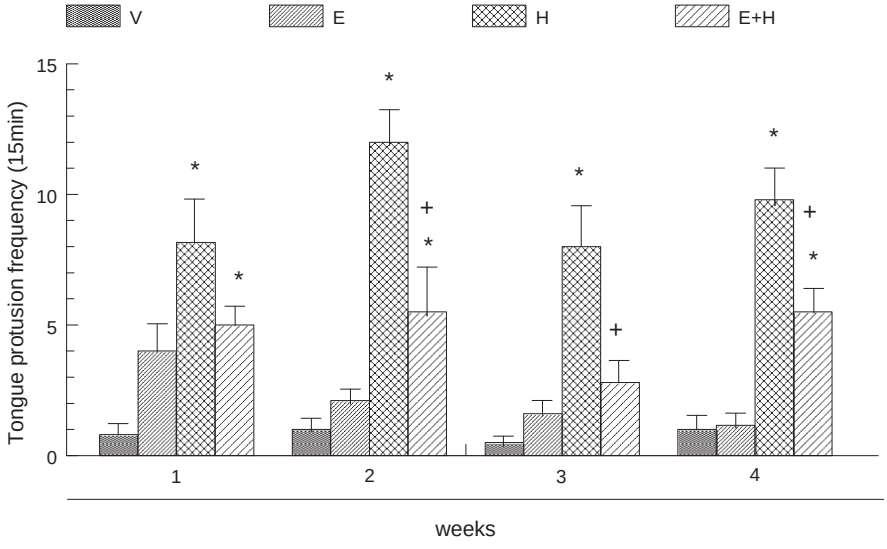

Fig. 1. Effects of administration of haloperidol (H, 12 mg/kg/week, sc for 4 weeks), vehicle (V), ebselen (E, 30 mg/kg, ip, in every other day) or ebselen plus haloperidol (E+H) on tongue protusion frequency. The first injection of ebselen or 1% Tween solution was given five days before the first injection of haloperidol or 1% tween solution. Univariate analysis revealed a significant effect of treatments (F (3,20)=7.7; 19.0; 17.8 and 23.1) (all p values <0.001), for week 1, 2, 3 and 4 respectively. *Indicates a significant difference from control group for $p<0.05$; and + indicates a significant difference from haloperidol-treated animals for a $p<0.05$ (Duncan's multiple range test).

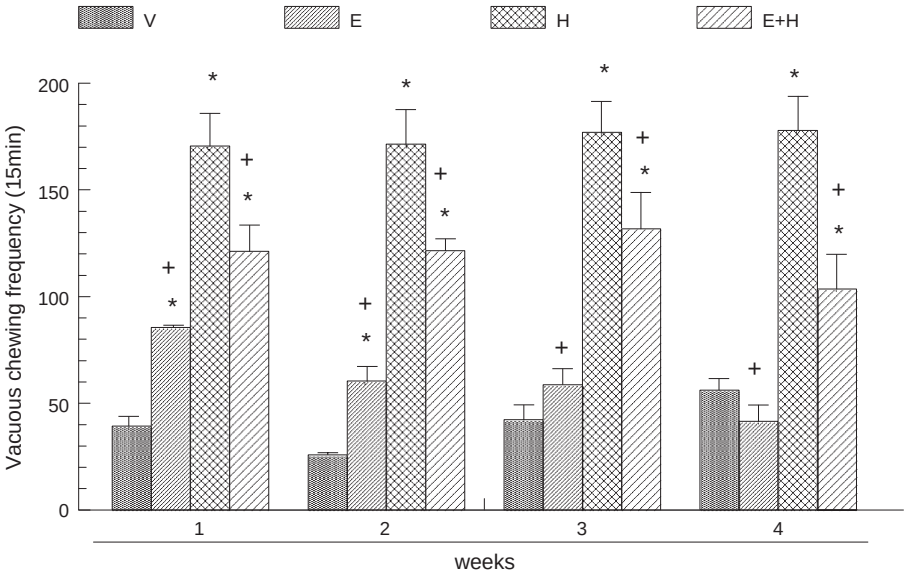

Fig. 2. Effects of administration of haloperidol (H, 12 mg/kg/week, sc for 4 weeks), vehicle (V), ebselen (E, 30 mg/kg, ip, in every other day) or ebselen plus haloperidol (E+H) on vacuous chewing frequency. The first injection of ebselen or 1% Tween solution was given five days before the first injection of haloperidol or 1% tween solution. Univariate analysis revealed a significant effect of treatments ($F(3,20)=30.2$; 36.8; 28.3 and 32.0) (all p values <0.001), for week 1, 2, 3 and 4 respectively. *Indicates a significant difference from control group for $p<0.05$; and + indicates a significant difference from haloperidol-treated animals for a $p<0.05$ (Duncan's multiple range test).

week of treatment and the difference disappeared as the treatment proceeded (Fig. 2).

Haloperidol treatment for 28 days induced lipid peroxidation in the cortex (Fig. 4a), striatum (Fig. 4b) and subcortical parts (Fig. 4c) when compared to the control group ($p<0.05$). Co-administration of ebselen and haloperidol significantly prevented the overproduction of TBARS levels in the cortex and striatum as compared to those of the haloperidol-group ($p<0.05$), but not in the subcortical parts (Fig. 4c).

4. Discussion

In the present study, haloperidol-treated animals developed orofacial dyskinesia, which was determined by an

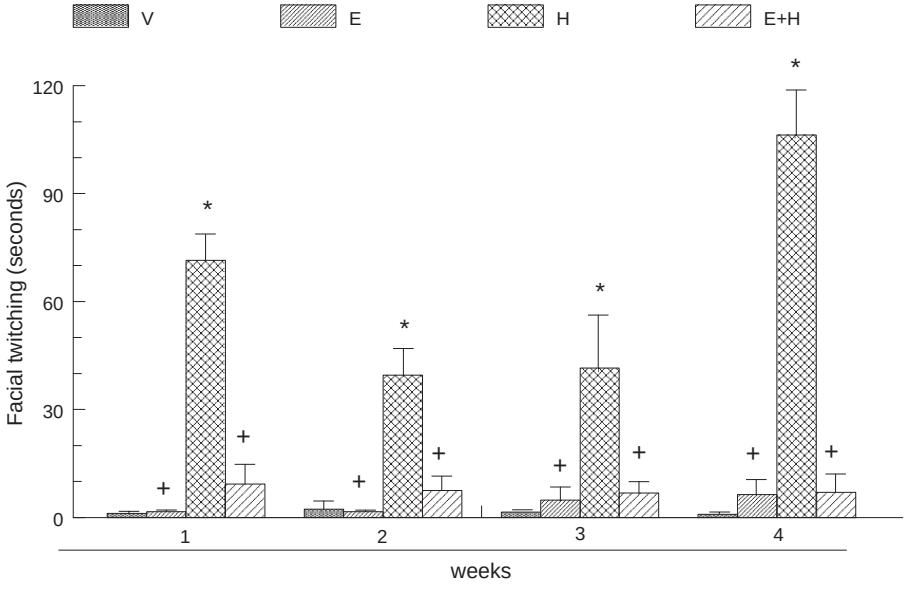

Fig. 3. Effects of administration of haloperidol (H, 12 mg/kg/week, sc for 4 weeks), vehicle (V), ebselen (E, 30 mg/kg, ip, in every other day) or ebselen plus haloperidol (E+H) on twitching of the facial musculature duration (in seconds). The first injection of ebselen or 1% Tween solution was given five days before the first injection of haloperidol or 1% tween solution. Univariate analysis revealed a significant effect of treatments ($F(3,20)=51.6$; 18.0; 10.9 and 87.9) (all p values <0.001), for week 1, 2, 3 and 4 respectively. *Indicates a significant difference from control group for $p<0.05$; and + indicates a significant difference from haloperidol-treated animals for a $p<0.05$ (Duncans multiple range test).

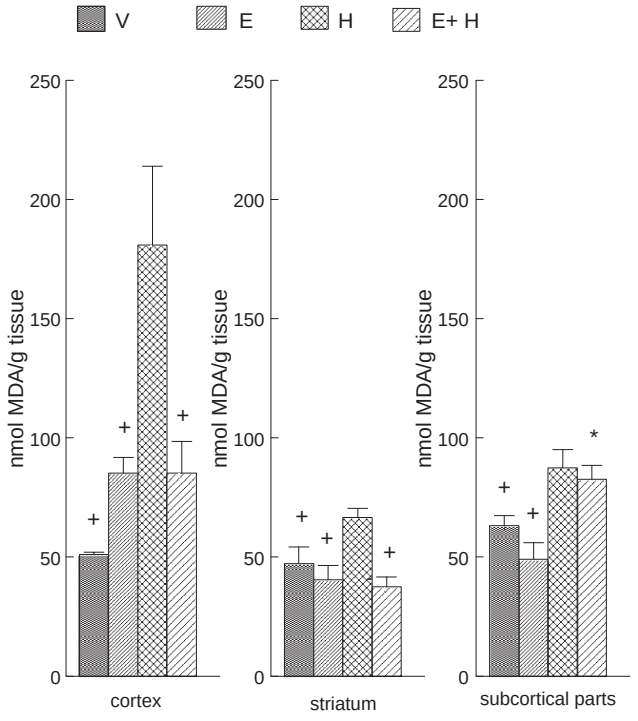

Fig. 4. Effects of administration of haloperidol (H, 12 mg/kg/week, sc for 4 weeks), vehicle (V), ebselen (E, 30 mg/kg, ip, in every other day) or ebselen plus haloperidol (E+H) on cortical (a), striatal (b) and subcortical parts (c) TBARS levels. The first injection of ebselen or 1% Tween solution was given five days before the first injection of haloperidol or 1% tween solution. Univariate analysis revealed a significant effect of treatments ($F(3,20)=7,6$; 10,85 and 7,8) (all p values <0.001). *Indicates a significant difference from vehicle (C) for $p<0.05$ (Duncan's multiple range test) and + indicates a significant difference from haloperidol group (H) for a $p<0.05$ (Duncan's multiple range test).

increase in VCMs, FT and TP. The administration of ebselen showed a protective effect against haloperidol-induced orofacial dyskinesia. Ebselen counteracted the increase in TP, VCM and FT caused by haloperidol treatment, at all the evaluation time points.

Literature data indicate that an imbalance production/detoxification of free radicals may be associated with chronic neuroleptic use and it contributes to the onset of tardive dyskinesia (Cadet et al., 1986). Typical neuroleptics block dopamine D2 receptors (Creese et al., 1976; Seeman et al., 1976) and this blockadge is associated with particularly increased dopamine turnover in catecholamine rich regions such as basal ganglia. Of particular importance, these regions of the brain are vulnerable to free radical overproduction caused by dopamine turnover, because they use elevated amounts of energy and contain considerable amounts of polyunsaturated fatty acids (Lohr et al., 2003b). The high oxidative metabolism in these regions after haloperidol may be associated with a reduction of antioxidant brain defenses, here detected by the reaction with thiobarbituric acid (TBARS). TBARS are only an indirect and approximate indicator of oxidative stress and can indicate the formation of other products that are not derived from lipid peroxidation. However, there are several points of evidence in the literature that an increase in TBARS can be correlated to an increase in other more direct measures of oxidative stress such as protein carbonyls and 8-oxo-2′-deoxyguanosine formation (Campos et al., 2005; Kasapoglu and Özben, 2001; Kashif et al., 2004; Kumaraguruparan et al., 2005; Öztürk and Gümüslü, 2004; Ramachandran et al., 2004; Rodrigo et al., 2005; Sahin and Gümüslü, 2004; Shivakumar and Ravindranath, 1993; Singh et al., 2004).

In the present study, haloperidol-treated animals showed increased levels of TBARS in some brain regions, when compared to vehicle-treated control animals. Our results from haloperidol-treated animals are in accordance with data from the literature showing increased TBARS levels in the brain of haloperidol treated rats (Polydoro et al., 2004; Naidu et al., 2003; Singh et al., 2003). Ebselen protected haloperidol-treated rats against the TBARS production in the cortex and striatum of rats. The antioxidant action of ebselen was not observed in subcortical parts of brain. This can be related to changes in the glutamate transport in this region. Recently, we demonstrated that rats treated with haloperidol developed orofacial dyskinesia and this correlated with a significant reduction in glutamate uptake in synaptosomes obtained from the subcortical parts of the brain, whereas no significant differences in glutamate uptake were observed in the cortical and striatal Synaptosomes (Burger et al., 2005). This may indicate that this part of brain is more vulnerable to excitotoxicity and/or oxidative stress and responds less to antioxidants than the other considered parts of the brain.

Using this and other experimental models, several groups of investigators have demonstrated that haloperidol treatment (Arnaiz et al., 1999) and oral diskynesia are closed associated with the oxidative stress process (Abilio et al., 2003a,b; Andreassen and Jorgensen, 1994; Bergamo et al., 1997; Calvente et al., 2002; Naidu et al., 2003; Perry et al., 2004; Raghavendra et al., 2001; Singh et al., 2003; Vital et al., 1998; Vital et al., 1997), as well as neuropathological alterations within the basal ganglia (Andreassen et al., 2003; Andreassen and Jorgensen, 2000) and structural alterations of dopaminergic neuronal architecture induced by haloperidol (Marchese et al., 2002). In line with this, Yokoyama et al. (1998) showed that free radicals play a causative role in TD, through the detection of lipid radicals and hydrogen peroxide in striatum of rats treated with haloperidol. Further support for the involvement of oxidative stress as a causative agent of orofacial diskinesia was recently obtained by Frussa-Filho and co-workers, where they showed that a decreased striatal catalase activity is involved in the development of orofacial dyskinesia in rats (Abílio et al., 2004).

Organic forms of selenium have been pointed out as possible antioxidant agents because they exhibit glutathione peroxidase-like activity and oxidized-SH during the reduction of H_2O_2 (Müller et al., 1985, Wendel et al., 1984). More

recently, the neuroprotective mechanism of ebselen has been related to its thioredoxin reductase activity (Zhao and Holmgren, 2002). Recently we showed the protective action of ebselen in an experimental model of orofacial dyskinesia induced by reserpine (Burger et al., 2003). The orofacial dyskinesia may be caused primarily by free radicals formed during catecolamine metabolism, including dopamine quinones and hydrogen peroxide produced by MAO (Lohr, 1991). These reactive species would subsequently promote lipoperoxidation and ebselen, via its glutathione peroxidase-like or thioredoxin reductase activity, could reduce it by decomposing peroxides.

5. Conclusion

Lipid peroxidation is an important outcome of neurotoxicity induced by a variety of agents and illnesses. In the present study, ebselen was able to reverse the behavioral changes caused by exposure to haloperidol and had a protective action against TBARS production induced by this widely used neuroleptic. Since literature data indicate that ebselen can be used in humans (Imai et al., 2001; Parnham and Sies, 2000; Saito et al., 1998; Tamaguchi et al., 1998; Yamaguchi et al., 1998), this organo-selenium compound should be considered for continuation of animal and possibly clinical studies as a potential therapeutic agent to prevent development of tardive diskynesia.

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