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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).