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Gallic acid decreases vacuous chewing movements induced by reserpine in rats

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ABSTRACT

Involuntary oral movements are present in several diseases and pharmacological conditions; however, their etiology and efficient treatments remain unclear. Gallic acid is a natural polyphenolic acid found in gall nuts, sumac, oak bark, tea leaves, grapes and wine, with potent antioxidant and antiapoptotic activity. Thus, the present study investigated the effects of gallic acid on vacuous chewing movements (VCMs) in an animal model induced by reserpine. Rats received either vehicle or reserpine (1 mg/kg/day, s.c.) during three days, followed by treatment with water or different doses of gallic acid (4.5, 13.5 or 40.5 mg/kg/day, p.o.) for three more days. As result, reserpine increased the number of VCMs in rats, and this effect was maintained for at least three days after its withdrawal. Gallic acid at two different doses (13.5 and 40.5 mg/kg/day) has reduced VCMs in rats previously treated with reserpine. Furthermore, we investigated oxidative stress parameters (DCFH-DA oxidation, TBARS and thiol levels) and Na^+,K^+-ATPase activity in striatum and cerebral cortex, however, no changes were observed. These findings show that gallic acid may have promissory use in the treatment of involuntary oral movements.

1. Introduction

Involuntary oral movements are important symptoms associated with several diseases or pharmacological conditions, such as Parkinson's disease or tardive dyskinesia, respectively (Andreassen and Jørgensen, 2000; Dauer and Przedborski, 2003; Lotharius and Brundin, 2002; Thomas and Beal, 2007). These movements are highly prevalent in the population around the world. It is worth mentioning that Parkinson's disease is the second most common neurodegenerative disease, affecting approximately 1–2% of the population over 65 years (Alves et al., 2008), while tardive dyskinesia has a prevalence of 24.2% in patients under chronic antipsychotic treatment (this number can change according to age, gender, antipsychotic class, etc.) (Yassa and Jeste, 1992). Up to now, the pathophysiology of the involuntary oral movements, as well as the efficient treatments, remain unclear (Andreassen et al., 2003; Lohr et al., 2003).

Several drugs, such as reserpine, a monoamine-depleting agent, have been used experimentally as an auxiliary in the study of involuntary oral movements. Literature data show that repeated administrations of reserpine increase the number of vacuous chewing movements (VCMs) in animal models (Abílio et al., 2004; Barcelos et al., 2011; Burger et al., 2003; Busanello et al., 2011; Fernandes et al., 2012; Neisewander et al., 1994; Pereira et al., 2011; Teixeira et al., 2008, 2009). It is suggested that oxidative stress, at least in part, is involved in VCMs pathophysiology (Abílio et al., 2003; Bilska and Dubiel, 2007; Burger et al., 2003; Fachinetto et al., 2005; Faria et al., 2005; Fernandes et al., 2012; Naidu et al., 2004; Teixeira et al., 2008, 2009). Accordingly, some studies have showed that reserpine administration decreases the levels of some antioxidant defenses and increases oxidative markers in animals (Abílio et al., 2003; Teixeira et al., 2008). Na^+,K^+-ATPase is an enzyme sensitive to oxidative stress status (Morel et al., 1998). However, the role of Na^+,K^+-ATPase activity has not been completely established in animal models of involuntary oral movements induced by reserpine in rats.

Recent studies have demonstrated that several natural antioxidants can minimize involuntary movements in reserpine-treated animals (Barcelos et al., 2011; Busanello et al., 2011; Castro et al., 2006; Faria et al., 2005; Pereira et al., 2011; Trevizol et al., 2011) and "in" other involuntary oral movement models (Barcelos et al., 2010; Bishnoi et al., 2008; Busanello et al., 2012; Naidu et al., 2003; Sachdev et al., 1999; Trevizol et al., 2011). Gallic acid (3, 4, 5-trihydroxybenzoic acid) is an important polyphenolic compound found in plants and foods (Eslami et al., 2010) especially in gallnuts, sumac, oak bark, green tea, grapes, strawberries, pineapples, bananas, lemons, witch hazel, red and white wines and apple peels (Chu et al., 2002; Wolfe et al., 2003). It has received attention because of its potent ability to scavenge ROS (Kim, 2007; Priscilla and Prince, 2009),

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antiapoptotic (Pal et al., 2010; Sameermahmood et al., 2010) and antitumoral activity (Inoue et al., 1994; Kawada et al., 2001; Serrano et al., 1998). Of particular importance to our present investigation, it was recently demonstrated that gallic acid treatment attenuated locomotor damage and brain oxidative stress induced by lead in rats (Reckziegel et al., 2011). Currently, there are no studies investigating the action of gallic acid in involuntary movements induced by reserpine. Thus, the aim of this study was to investigate the effects of gallic acid on VCMs, oxidative stress parameters, and Na^+,K^+-ATPase activity in rat cerebral cortex and striatum after reserpine treatment.

2. Materials and methods

2.1. Animals

Adult male Wistar rats (220–270 g) were kept in a room with controlled temperature (22 ± 2 °C) and under a 12 h light/dark cycle (lights on at 7:00 am). Food and water were provided *ad libitum*. All experiments were performed in accordance to the guidelines of the Nacional Council of Control of Animal Experimentation (CONCEA). This protocol was approved by the Ethics Commission on Animal Use of the Federal University of Santa Maria under process number 010/2012.

2.2. Drugs

All reagents were purchased from Sigma (Sigma-Aldrich, St. Louis, MO, USA). Reserpine (methyl reserpate 3, 4, 5-trimethoxybenzoic acid ester) was dissolved in saline solution containing 0.2% acetic acid and its vehicle consisted of the same preparation without reserpine. Gallic acid (3, 4, 5-trihydroxybenzoic acid) was dissolved in Milli-Q water, protected from light and used within 10 min from preparation. All solutions were administrated to the animals in a constant volume of 1 ml/kg body weight.

2.3. Experimental design

Rats were treated with either 1 mg/kg reserpine (n = 37) or its vehicle (n = 31) subcutaneously once a day (8:00 am) for 3 consecutive days. After this treatment (day 4), rats from each group were subdivided into 4 groups and treated by gavage with either water or different doses of gallic acid (4.5, 13.5 or 40.5 mg/kg/day, divided in two daily administrations at 8:00 a.m. and 5:00 p.m.) for 3 consecutive days (Fig. 1). The experimental groups were as follows: control (C, n = 10), 4.5 mg/kg gallic acid (GA, 4.5 mg/kg/day, n = 5), 13.5 mg/kg gallic acid (GA, 13.5 mg/kg/day, n = 11), 40.5 mg/kg gallic acid (GA, 40.5 mg/kg/day, n = 5), reserpine (R, 1 mg/kg/day n = 12), reserpine plus 4.5 mg/kg gallic acid (R + GA, 4.5 mg/kg/day, n = 6), reserpine plus 13.5 mg/kg gallic acid (R + GA, 13.5 mg/kg/day, n = 13), and reserpine plus 40.5 mg/kg gallic acid (R + GA, 40 mg/kg/day n = 6).

2.4. Behavioral test — quantification of VCMs

The number of VCMs was evaluated before each treatment (day 0) (animals that spontaneously presented more than 20 VCMs during a 6 minute observation period were not included in the study). Subsequent evaluations were carried out on days 4 (14 h after the last reserpine injection) and 7 (14 h after the last gallic acid administration) (Fig. 1).

To quantify the VCMs, the rats were placed individually in glass cages (20 × 20 × 19 cm) containing one movable mirror under the floor to permit the observation of VCMs when the animals were away from the observer. The VCMs were recorded during 6 min after a 6 minute acclimation period, according to the previously published method (Fachinetto et al., 2005, 2007a,b; Busanello et al., 2012). VCM is defined as a single mouth opening on the vertical plane not directed toward physical material. If VCMs occurred during a period of grooming, they were not taken into account. After each test, the cages were cleaned with 30% alcohol solution to eliminate possible odors and prevent the next animal from smelling the previous one. Experimenters were always blind to treatments.

2.5. Tissue preparation and biochemical assays

After the last behavioral test, on day 7, the animals were killed by decapitation and the brains were rapidly dissected and placed into a Petri dish on ice. Cortical and striatal tissues were dissected and homogenized in 10 volumes (w/v) of 30 mM Tris–HCl, pH 7.4, and then centrifuged (3000 rpm/10 min). The resulting supernatants were used in biochemical assays described below. Brain regions were chosen according to the neuropathology associated with VCM development that has been described in striatum especially in ventrolateral striatum (Kelley et al., 1989; Salamone et al., 1998). On

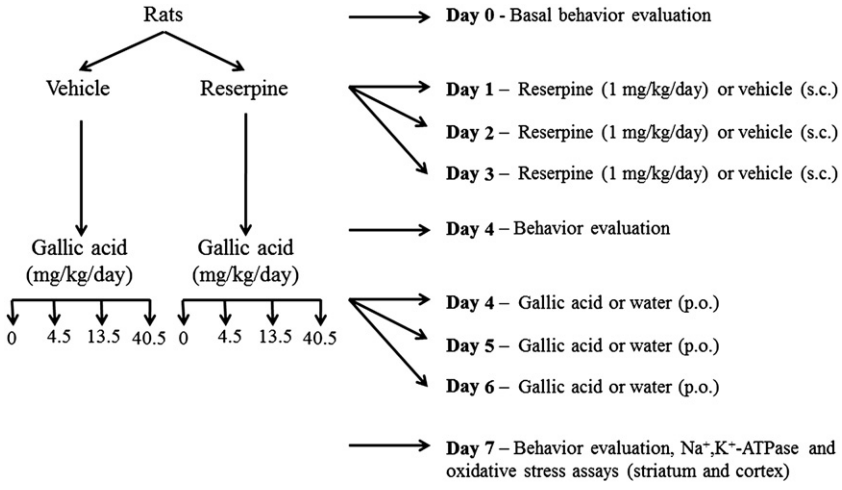

Fig. 1. Experimental design. Rats were treated with saline or reserpine (1 mg/kg/day, s.c.) during 3 days. After treatment (day 4), rats from each group were divided in 4 subgroups and treated by gavage with water or different doses of gallic acid (4.5, 13.5 or 40.5 mg/kg/day, p.o.). The experimental groups were as follows: control (C, n = 10), 4.5 mg/kg gallic acid (n = 5), 13.5 mg/kg gallic acid (n = 11), 40.5 mg/kg gallic acid (n = 5), reserpine (n = 12), reserpine plus 4.5 mg/kg gallic acid (n = 6), reserpine plus 13.5 mg/kg gallic acid (n = 13) and reserpine plus 40.5 mg/kg gallic acid (n = 6). Striatum and cortex were used for biochemical assays of DCFH-DA oxidation, TBARS, thiols and Na^+,K^+-ATPase. Behavior evaluations were performed on days 0, 4 and 7.