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ScienceDirect
Pharmacology, Biochemistry and Behavior 88 (2008) 465–472
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Influence of chronic exercise on reserpine-induced oxidative stress in rats: Behavioral and antioxidant evaluations

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Received 5 March 2007; received in revised form 24 August 2007; accepted 10 October 2007
Available online 16 October 2007

Abstract

Several neurological diseases are related to oxidative stress (OS) and neurotoxicity. Considering that physical exercise may exert beneficial effects on antioxidant defenses, our objective was to evaluate the influence of a swimming exercise on an OS animal model (reserpine-induced orofacial dyskinesia). In this model, the increased dopamine metabolism can generate OS and neuronal degeneration, causing involuntary movements. The increase in vacuous chewing movements and facial twitching caused by reserpine (1 mg/kg sc) was partially prevented by exercise. An increase in catalase activity and a decrease in GSH levels were observed in the striatum. Physical training did not change the effects of reserpine on catalase, however it partially recovered GSH. Exercise *per se* caused a significant GSH decrease. There was a positive correlation between catalase and OD ($r=0.41$; $r=0.47$, $P<0.05$) and a negative correlation between GSH and OD ($r=0.61$; $r=0.71$, $P<0.05$). These results reveal the benefit of exercise in attenuating the motor disorder related to OS.

Keywords: Exercise; Orofacial dyskinesia; Reserpine; Oxidative stress; Excitotoxicity

1. Introduction

Physical activity is recognized as an important component of a healthy life style and is recommended by clinicians and scientists (Donaldson, 2000). The favorable effects of exercise on the cardiovascular system and on cognition suggest its influence on brain function (Cotman and Engesser-Cesar, 2002; Fordyce and Wehner, 1993; Hicks and Birren, 1970). Alterations elicited by exercise are associated with improvements in a variety of age-related diseases. However, the mechanisms are not yet well understood (Blair et al., 1995; Gündüz et al., 2004; Holloszy, 1993). Furthermore, habitual exercise has been related to OS resistance and the inhibition of carcinogenesis at the initiation stage (Nakatani et al., 2005).

Exercise is also associated with an increase of oxygen uptake (Sen, 2001), of which as much as 2% may be converted to reactive oxygen species (ROS) (Inoue et al., 2003; Wickens, 2001). However, this increased uptake of oxygen that occurs in the body is not observed in the brain and it has been reported that chronic exercise caused an increase in the brain's antioxidant defenses (Liu et al., 2000). The few studies available on the effect of exercise on oxidative damage or the antioxidant status in brain show conflicting results (Asha and Kiran, 2004; Radak et al., 1995; Somani et al., 1995). Suzuki et al. (1983) reported that voluntary exercise increased the lipid peroxidation in the brain of rats. On the other hand, regular exercise attenuated an age-associated decline in memory and reduced the accumulation of proteins affected by oxidative damage in the brain (Radak et al., 2001a,b). In line with this, regular physical exercise has been related to an increase in the number of new

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doi:10.1016/j.pbb.2007.10.004

hippocampal cells (Van Praag et al., 1999a,b), an increase in brain plasticity (Cotman and Berchtold, 2002), an increase in the production of neurotrophic factors (Neeper et al., 1996; Ogonovszky et al., 2005), and an increase in learning and memory (Fisher et al., 2000; Ogonovszky et al., 2005; Radak et al., 2001a, 2006; Van Praag et al., 1999a).

Of particular importance, the brain is more susceptible to oxidative damage when compared to other organs or systems (Halliwell and Gutteridge, 1999), mainly because it contains high levels of membrane lipids, excitotoxic amino acids, low levels of antioxidant defenses and autoxidizable neurotransmitters. For instance, dopamine (DA) reacts with molecular oxygen to form dopamine-quinones which can deplete glutathione, generating ROS during this process (Graham, 1978). When the production of ROS exceeds the ability of the antioxidant system to eliminate them, oxidative damage results (Jenkins and Goldfarb, 1993). Considering the OS, reserpine is a monoamine depletor that exerts a blockade on the vesicular monoamine transporter (VMAT) for neuronal transmission or storage, promoting dopamine-autoxidation and oxidative catabolism by monoamine oxidase (MAO) (Fuentes et al., 2007). This accelerated mechanism leads to the formation of dopamine-quinones and hydrogen peroxide, related to the OS process (Abílio et al., 2002, 2003a; Bilzka and Dubiel, 2007; Burger et al., 2003; Calvente et al., 2002; Naidu et al., 2004; Spina and Cohen, 1988, 1989). In particular, areas of the brain, such as the basal ganglia, are rich in monoamines and therefore more vulnerable to free radical damage that may result in OS (Lohr et al., 2003). The neuronal damage of the basal ganglia is associated with damage of voluntary movements (Dawson et al., 2000; Graybiel et al., 1995) and related to different diseases such as Huntington, ballism, Parkinson and tardive dyskinesia (Albin et al., 1989; Andreassen and Jorgensen, 2000; Bartzokis et al., 1999; Fahn and Cohen, 1992; Gilgun-Sherki et al., 2001; Lohr et al., 1990).

Various laboratories have demonstrated the development of a movement disorder upon the administration of reserpine in rats/mice (Abilio et al., 2002, 2003b, 2004; Bergamo et al., 1997; Burger et al., 2003, 2004, 2005b; Calvente et al., 2002; Carvalho et al., 2003; Castro et al., 2006; Colpaert, 1987; Dawson et al., 2000; Dutra et al., 2002; Menzaghi et al., 1997; Naidu et al., 2004; Neisewander et al., 1994; Peixoto et al., 2005; Queiroz and Frussa-Filho, 1999; Raghavendra et al., 2001; Silverdale et al., 2001; Sussman et al., 1997; Vital et al., 1997). This animal model, known as orofacial dyskinesia, has been related to OS in the basal ganglia (striatum) and is attenuated and prevented by antioxidant substances such as melatonin, ebselen and quercetin (Abílio et al., 2002, 2003a,b; Burger et al., 2003, 2004, 2005b; Faria et al., 2005; Naidu et al., 2004; Raghavendra et al., 2001).

As the brain is particularly vulnerable to free radical damage and the enhancement of OS has been associated with various neurodegenerative diseases, we investigated the effects of an exercise program in an animal model of OS and its relationship with the antioxidant defenses. Smith and Zigmond (2003) considered that exercise afforded protection against a variety of diseases including Parkinson and dopaminergic degeneration. In the same way, Howells et al. (2005) demonstrated that voluntary exercise afforded neuroprotection in a Parkinson's disease rat model. With this in mind, our objective is to evaluate whether chronic physical exercise is capable of attenuating or preventing neuronal damage related to reserpine-induced OS.

2. Method

2.1. Drugs

Reserpine (methyl reserpate 3,4, 5-trimethoxybenzoic acid ester—Sigma Chemical) was dissolved in glacial acetic acid and then diluted to a final concentration of 0.5% acetic acid with distilled water. The vehicle consisted of a 0.5% acetic acid solution. These solutions were injected subcutaneously (sc) in a volume of 1.0 ml/kg body weight.

2.2. Animals

Male Wistar rats weighing 270–320 g (about 3-month of age) were used. Groups of six animals were kept in Plexiglas cages with free access to food and water in a room with controlled temperature (22–23 °C) and on a 12 h-light/dark cycle with lights on at 7:00 a.m. 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. The rats were randomly assigned into four groups: sedentary-control (SC), sedentary-reserpine (SR), exercise-control (EC), exercise-reserpine (ER).

2.3. Training and experimental procedure

All rats from the exercise groups were subjected to swimming in a plastic container (depth 45 cm) and continuously supervised, with the water temperature set to 28 °C ± 1 °C, 1 h/day, 5 times per week during 8 weeks. The swimming duration increased about 15 min every day until it reached 60 min per day in the first week, which was maintained until the sixth week; in the seventh and eighth week they swam 90 min/day. The control rats (sedentary) were transported to the experimental room and placed in the swimming pool for a short time (3 min), to force them to get wet, however, they were not in contact with water for the same time that the swimmers were. One day after the last training, all the animals were treated with vehicle or reserpine solution. The drugs were then subcutaneously administered, for 3 days every other day, as follows:

SC sedentary rats injected with 0.5% acetic acid solution (vehicle for reserpine);
SR sedentary rats injected with 1 mg/kg reserpine solution;
EC exercised rats injected with 0.5% acetic acid solution;
ER exercised rats injected with 1 mg/kg reserpine solution.

On the fourth day, 24 h after the second reserpine or vehicle injection, all the rats were observed for the quantification of

orofacial dyskinesia. The animals were decapitated 24 h after behavioral measurements.

The animal's body weights were monitored once a week during the experiment.

2.4. Behavioral testing

With the objective of analyzing the development of reserpine-induced orofacial dyskinesia, the rats were submitted to behavioral observation as follows: 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 vacuous chewing movements (VCM) and the duration of facial twitching (FT) were recorded during 10 min. Observers were blind to the drug treatment. In a preliminary study (using 5 control and 10 rats treated with reserpine) of interrater reliability, we found that the use of this method of observation and definition for the parameters evaluated usually resulted in >90 and 91% agreement between 4 different observers for vacuous chewing and duration of facial twitching, respectively. All the calculated P values were significant for $P<0.05$.

2.5. Biochemical assays

The brains were removed immediately after decapitation, put on ice and cut coronally at the caudal border of the olfactory tubercle. The striatum was dissected from the anterior part and separated into two parts. The right striatum was homogenized in 10 volumes (w/v) of 0.1 M Tris–HCl, pH 7.4, centrifuged for 10 min at 3000 ×g, and used for catalase determination by spectrophotometry (Aebi et al., 1995).

The left striatum was homogenized in 50 volumes (w/v) of 0.5 N perchloric acid and centrifuged under the same conditions previously cited. The supernatant was used to measure reduced glutathione (GSH). A volume of 130 µl of supernatant was mixed with 500 µl of Tris–HCl 0.5 M. The derivatization of the samples was carried out with 350 µl DTNB (5.5′-dithiobis(2-nitro-benzoic acid) for high performance liquid chromatography (Schott et al., in press).

2.6. Statistical analysis

Data were analyzed by two-way ANOVA (2 (sedentary/exercise)×2 (control/reserpine) followed, when appropriate, by univariate analysis and Duncan's multiple range test.

3. Results

Eight weeks of swimming did not cause a difference in body weight between exercised and control animals, which is in accordance with other research using swimming as an exercise model (Gündüz et al., 2004; Radak et al., 2001a).

Two-way ANOVA of vacuous chewing frequency revealed a significant main effect of reserpine [$F(1, 20)=136.6$, $P<0.001$]. Univariate ANOVA followed by Duncan's multiple range test revealed that reserpine (SR) and exercise+reserpine (ER)-treated groups displayed an increase in vacuous chewing frequency when compared to control (SC) and exercise-treated (EC) groups (Fig. 1A).

Analyses of the duration of facial twitching yielded a significant main effect of reserpine [$F(1,20)=57.6$, $P<0.001$],

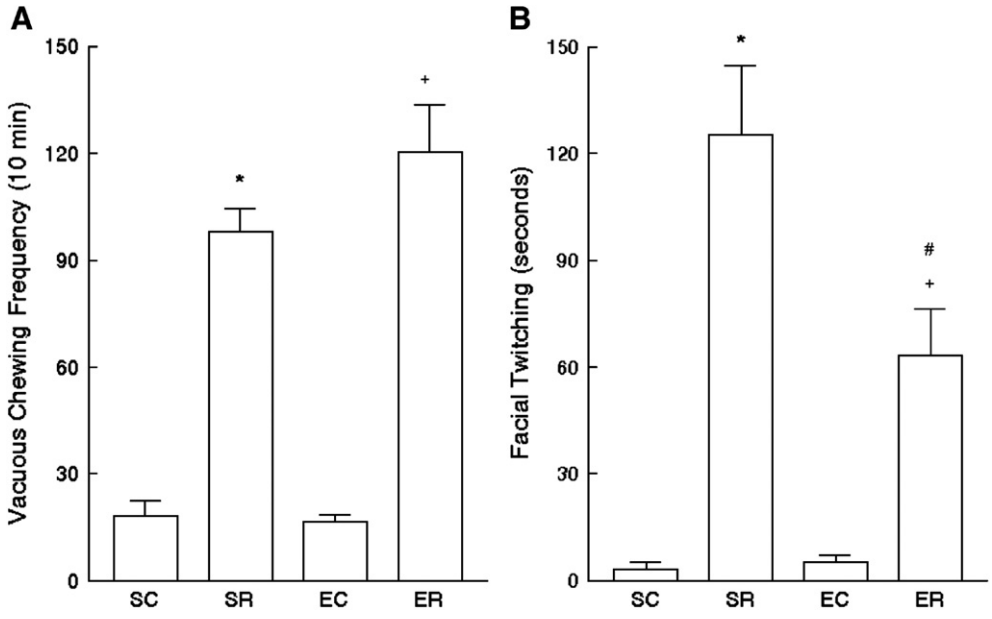

Fig. 1. Effects of administration of reserpine (1.0 mg/kg sc every other day, for 3 days) (SR) or vehicle (SC) on sedentary rats and rats submitted to exercise training (ER) or (EC) for vacuous chewing frequency (A) and duration of twitching of the facial musculature (in seconds) (B). Data (mean±SEM) were analyzed by one-way analysis of variance followed by Duncan's test. * indicates a significant difference from control group (SC) for $P<0.001$, $^{+}$ indicates a significant difference from exercised rats (EC) for $P<0.05$, and $^{\#}$ indicates a significant difference from reserpine-treated animals (SR) for $P<0.05$ (Duncan's multiple range test).

Table 1
Catalase activity (mU/g tissue) and GSH levels (mM/g tissue) in the striatum of rats as the result of chronic exercise training

	SC	SR	EC	ER
	$n=6$	$n=6$	$n=6$	$n=6$
Catalase activity	1.95±0.16	2.51±0.16*	1.81±0.1	2.21±0.13
GSH levels	3.17±0.12	1.26±0.1**	2.18±0.1**	2.07±0.13^{+}

Values are means±SEM, *$P<0.05$, **$P<0.001$, differences from sedentary-control group (SC); $^{+}P<0.001$, difference from sedentary-reserpine group (SR) (Duncan's multiple range test).

exercise [$F(1, 20)=6.4$, $P<0.05$] and a significant reserpine×exercise interaction [$F(1, 20)=7.2$, $P<0.05$]. Univariate ANOVA followed by Duncan's multiple range test revealed that reserpine considerably increased the duration of facial twitching and that the exercise training partially reversed the effect of reserpine. In fact, the duration of facial twitching for the exercise+reserpine-treated animals (ER) was significantly lower than that of rats treated with reserpine (SR) and significantly higher than that of control (SC) or exercise-treated (EC) animals (Fig. 1B).

Two-way ANOVA of catalase activity is shown in Table 1. Two-way ANOVA revealed a significant main effect of reserpine on catalase activity [$F(1, 20)=12.8$, $P<0.05$]. Univariate ANOVA followed by Duncan's multiple range test revealed that reserpine significantly increased catalase activity (SR) and that chronic exercise training did not reverse the effect of reserpine (ER).

Two-way ANOVA for GSH (Table 1) revealed a significant reserpine effect [$F(1, 20)=109.22$, $P<0.001$] as well as exercise×reserpine interaction [$F(1, 20)=86.74$, $P<0.001$]. Post-hoc analysis revealed that rats treated with reserpine (SR), exercise (EC) and exercise+reserpine (ER) presented a decrease in GSH levels when compared to controls (SC). The animals that received the exercise-reserpine (ER) co-treatment showed a partial recovery of GSH levels, when compared to the group treated with reserpine (SR).

Statistical analyses revealed a significant positive correlation between vacuous chewing frequency ($r=0.41$, $P<0.05$, Fig. 2) and facial twitching ($r=0.47$, $P<0.05$, Fig. 2) with striatal catalase activity of rats. To the contrary, regression analyses between vacuous chewing frequency ($r=0.61$, $P=0.001$ Fig. 3) and facial twitching ($r=0.71$, $P<0.001$, Fig. 3) with GSH levels in the striatum of rats revealed a significant negative correlation.

4. Discussion

The results of the present study clearly indicate that moderate chronic physical exercise is capable of exerting a protective role against reserpine-induced orofacial dyskinesia, shown through increased vacuous chewing movements and facial twitching. Exercise training partially reversed the increase in FT duration and, interestingly, did not change VCM frequency. This result is in accordance with other findings from our laboratory, where ebselen (an antioxidant agent) reversed the reserpine-induced increase in FT but did not modify VCM (Burger et al., 2003).

Of particular interest for the animal model chosen here, different laboratories have associated OS with neurodegeneration and movement disorders (Cadet et al., 1986, Cadet and Kahler, 1994; Naidu et al., 2003; Post et al., 1998; Sagara, 1998;), and have searched for antioxidant substances (Abílio et al., 2002, 2003a,b; Burger et al., 2003, 2005a; Dabiri et al., 1994; Egan et al., 1992; Faria et al., 2005; Naidu et al., 2003; Raghavendra et al., 2001; Singh et al., 2003). In fact, Sussman et al. (1997) showed that reserpine administration causes a decrease in striatal dopamine levels and an increase in the

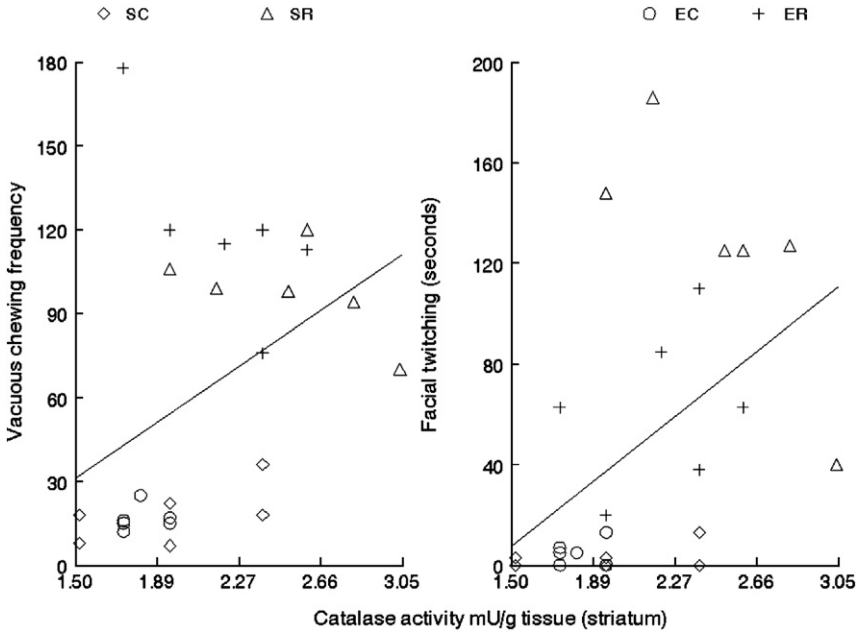

Fig. 2. Linear regression analysis between vacuous chewing frequency, facial twitching and catalase activity in the striatum of rats treated with reserpine (1.0 mg/kg sc every other day, for 3 days) following 8 weeks of chronic exercise training. (Statistical analysis revealed the following *P* significance levels for the *r* values: 0.41 and 0.47 respectively).

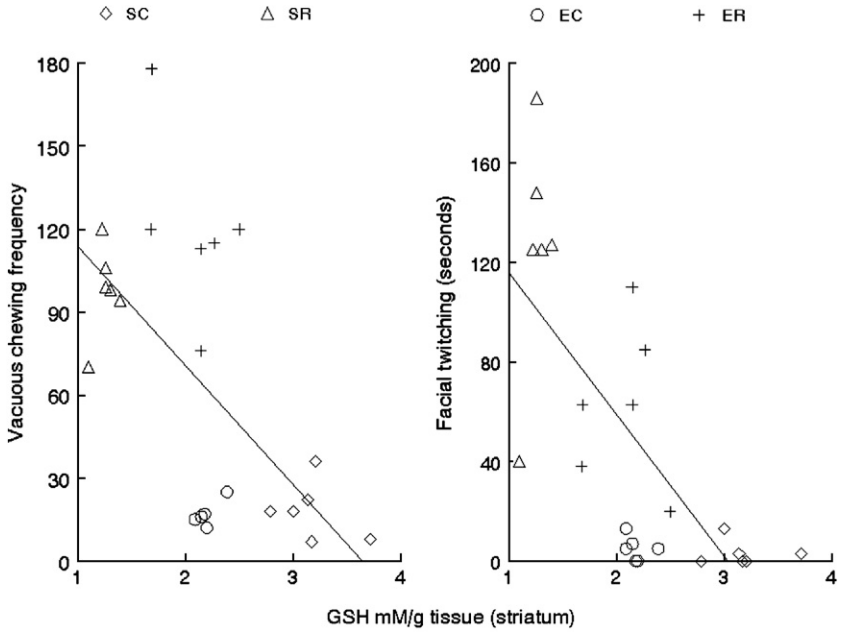

Fig. 3. Linear regression analysis between vacuous chewing frequency, facial twitching and GSH levels in the striatum of rats treated with reserpine (1.0 mg/kg sc every other day, for 3 days) following 8 weeks of chronic exercise training. (Statistical analysis revealed the following *P* significance levels for the *r* values: 0.61 and 0.71 respectively).

metabolite of dopamine ratios (DOPAC/dopamine and HVA/dopamine) in rats. Recently, we showed a negative relationship between the glutamate transporter and the manifestation of orofacial dyskinesia in rats exposed to reserpine or haloperidol (Burger et al., 2005b), contributing to the relation between OS and excitotoxicity. Coyle and Puttfarcken (1993) considered that these events may very well act together, since they are closely related. In line with this, the basal ganglia, involved in motor function, is particularly more vulnerable to free radical damage, since this brain region is rich in transition metals and contains large amounts of catecholamines such as dopamine. The antioxidant enzymes SOD, CAT and GSH-Px and the ratio of GSH to oxidized glutathione (GSSG) are critical for protection against oxyradical toxicity. Glutathione in its reduced state plays an important role in cellular protection against damage from free radicals and oxyradicals (Werner and Cohen, 1993), and its deficiency leads to mitochondrial damage in the brain (Jain et al., 1991).

Physical exercise early in life may be protective against the development of Parkinson's disease (PD) (Brasted et al., 1999; Sasco et al., 1992) and it ameliorates motor symptoms and neurochemical deficits in rodent models of induced striatal damage (Tillerson et al., 2003). In addition, symptoms of senile dementia might be improved by exercise (Sutoo and Akiyama, 2003) and may also protect against a variety of neurodegenerative conditions (Döbrössy and Dunnett, 2003; Smith and Zigmond, 2003).

Considering neurological diseases and OS, we found it interesting to examine whether moderate chronic exercise training changed the effect of repeated reserpine treatment in striatal catalase activity and GSH levels.

The results presented here demonstrate that reserpine administration increased catalase activity in the striatum. Recently, Abilio et al. (2004) and Faria et al. (2005) demonstrated the critical role of this antioxidant enzyme in the development of oral dyskinesia and OS. In line with this, it has been reported that catalase activity is low in the brain (Gaunt and De Duve, 1991), however, chronic physical exercise did not modify its activity. Of particular importance for the increase in free radicals induced by reserpine, the increased catalase activity found here may be a compensatory response or a signaling mechanism of an oxidative damage (Gomez-Cabrera et al., 2006).

We also demonstrated that reserpine reduced striatal GSH levels and this result occurred in parallel to an increase in orofacial dyskinesia. This negative correlation reinforces the role of free radicals in this putative animal model. In this study, the effect of reserpine on GSH levels was partially prevented by moderate physical training, although exercise *per se* reduced these levels and deserves further investigations. Abilio et al. (2003b) demonstrated a relationship between the development of reserpine-induced orofacial dyskinesia and an increase of the striatal GSSG/GSH ratio, where both effects were attenuated by vitamin E. These results show clearly that physical training is capable of exert beneficial effects on this important brain defense system. Different from our results, Somani et al. (1995) and Liu et al. (2000) did not observe the influence of exercise training on GSH levels in the striatum of rats, although the experimental procedures used were different. In reserpine-treated mice, a considerable rise was reported in the striatal GSSG level (Spina and Cohen, 1989) as well as in striatum and prefrontal cortex of rats (Bilska and Dubiel, 2007).

Swimming was chosen as the model of exercise over the treadmill since it is a natural behavior of rodents (Kramer et al., 1993; Venditti and Di Meo, 1996). It is less stressful and can prevent foot injury, which may generate ROS unrelated to exercise (Venditti and Di Meo, 1996). In this sense, the exercise

program and water temperature employed here were not stress factors, as demonstrated by the reduced facial twitching. In fact, the influence of stress has been demonstrated to elevate orofacial movements (Andreassen et al., 1996; Egan et al., 1996; Glenthoj et al., 1990, 1993; Glenthoj and Hemmingsen, 1991; Levy et al., 1987; Waddington, 1990). In addition, different animal models have associated oxidative damage to stress, including cold stress (Kaushik and Kaur, 2003; Liu et al., 1996; Madrigal et al., 2001; Sahin and Gümüslü, 2004a,b; Voronych and Iemel'ianenko 1994), corroborating with our results.

In conclusion, in this study, through the measurement of orofacial dyskinesia we have demonstrated for the first time that chronic moderate physical exercise reduces reserpine-induced OS and attenuates the reserpine-induced decrease in striatal GSH levels. These results establish the beneficial effect of exercise on special clinical disorders associated with movement such as Huntington and Parkinson diseases, tardive dyskinesia, ballism and other neurological diseases.

Acknowledgments

The financial support by FAPERGS, CAPES and CNPq is gratefully acknowledged.

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