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Intense exercise potentiates oxidative stress in striatum of reserpine-treated animals

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ABSTRACT

Regular physical activity exerts beneficial effects for mental and physical health, but an intense exercise can cause oxidative stress (OS) in dopaminergic regions and intensify the harmful effects of reserpine. Reserpine-induced neurotoxicity can be accessed by behavioral and biochemical evaluations. The objective of this study was to examine the effect of a gradual intensifying exercise program on an animal model of oxidative stress. Male rats were submitted to swimming sessions (1 h/day, for eleven weeks), and they were loaded gradually during the adaptation period (two weeks) with a weight corresponding to 1–7% of their body weight tied to their back. After the last training, the animals were treated with two doses of vehicle or reserpine (1 mg/kg-sc), an agent that induces orofacial dyskinesia. After behavioral evaluations, the striatum was dissected for enzymatic and biochemical assays. Development of cardiac hypertrophy demonstrated the effectiveness of the physical training. The gradual intense exercise and reserpine increased lipid peroxidation and striatal catalase activity. The results confirm the importance of catalase activity in orofacial dyskinesia which can be related to lipid peroxidation in striatal dopaminergic brain tissue. These results indicate that intense exercise can have some deleterious effect on striatal dopaminergic system.

1. Introduction

Regular physical exercise exerts many benefits for mental and physical health, reducing disease incidence, improving cognitive processes and increasing resistance to brain injury (Griesbach et al., 2004; Ogonovszky et al., 2005; Radak et al., 2001). Accumulated evidence has shown that regular physical activity may increase antioxidant defenses against brain oxidative damage (Radak et al., 2006; Somani et al., 1995) and induce resistance to oxidative stress (OS) (Banerjee et al., 2003; Ji, 1999) promoting antiapoptotic effects (Toldy et al., 2005). In this sense, moderate physical activity can offer protection against seizures (Setkowicz and Mazur, 2006; Dubow and Kelly, 2003), neurodegenerative diseases (Howells et al., 2005; Kiraly and Kiraly, 2005; Smith and Zigmond, 2003; Sutoo and Akiyama, 2003; Sasco et al., 1992), and alleviate symptoms of anxiety or depression (Martinsen et al., 1985).

Literatures data about the effect of regular exercise on brain oxidative stress (OS) and brain functioning have been conflicting (Radak et al., 2001; Suzuki et al., 1983). Indeed, part of literature supports a beneficial influence while other portion supports a deleterious effect of exercise. Considering different forms and intensity of physical activity, some research groups have demonstrated a relationship between exhaustive exercise and the increased generation of reactive oxygen species (ROS) in different biological tissues (Bejma et al., 2000; Reid et al., 1992; Sastre et al., 1992). In addition, excessive physical activity increased abruptly may generate psychological symptoms that resemble clinical depression (Armstrong and Van Heest, 2002; Budgett, 1998; Petibois et al., 2003) and a stress-related condition that may alter physiological and immunological functions associated with biochemical abnormalities (Angeli et al., 2004).

Of particular importance, the brain is more susceptible to OS when compared to other organs or systems, because it contains high content of unsaturated membrane lipids, excytotoxic amino acids, low levels of antioxidant defenses and autoxidizable neurotransmitters (Halliwell and Gutteridge, 1999). Free radicals are formed in the central nervous system (CNS) as part of normal metabolic processes (Halliwell, 1992), but when the production of ROS exceeds the ability of the antioxidant system to eliminate them, oxidative damage occurs (Jenkins and Goldfarb, 1993). This subject is extremely important since the brain is exposed throughout life to OS and there is evidence of the involvement of free radicals,over production in the pathophysiology of several diseases of the nervous system (Gilgun-Sherki et al., 2001). Among these diseases are included Alzheimer's (Pappolla et al., 1998), Parkinson's (Offen et al., 1999; Ziv et al., 1994), Huntington's (Browne et al., 1997), schizophrenia (Mahadik and Scheffer, 1996) and tardive dyskinesia (Tsai et al., 1998).

Reserpine is a monoamine depletor which prevents the storage of dopamine (DA) in neuronal synaptic vesicles. Reserpine interferes with the vesicular monoamine transporter (VMAT), causing an increase in

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cytosolic DA that can be oxidatively metabolized by MAO. This accelerated DA metabolism can lead to the formation of reactive metabolites and hydrogen peroxide, which can be associated with the OS process in dopaminergic neurons (Abílio et al., 2003a; Bilska and Dubiel, 2007; Burger et al., 2003; Naidu et al., 2004). Furthermore, autoxidation of DA produce *O*-quinone aminochrome that can suffer one-electron reduction to form the leukoaminochrome *O*-semiquinone radical, which is thought to be one of the major sources of endogenous reactive species involved in the degenerative processes (Fuentes et al., 2007; Paris et al., 2001, 2005; Segura-Aguilar et al., 2002). Particularly, the brain basal ganglia are rich in monoamines and therefore more vulnerable to free radical damage leading to OS (Lohr et al., 2003).

Experimentally, reserpine has been used by various laboratories to study movement disorder related to OS and neurodegenerative disease (Abílio et al., 2003b; Bilska and Dubiel, 2007; Castro et al., 2006; Dutra et al., 2002; Naidu et al., 2004; Peixoto et al., 2005). Recently, our laboratory has shown the beneficial effects of moderate chronic exercise on behavioral and biochemical parameters in an animal model of reserpine-induced OS (Teixeira et al., 2008). In view of the conflicting data found in the literature, the aim of the present study was to evaluate behaviorally and biochemically the influence of a gradual intense physical activity on brain susceptibility to OS, either alone or in association with reserpine, an OS-inductor. Particular attention was given to catalase in view of the recent studies of Abilio et al. (2004), which have shown an association between OD and catalase activity.

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 0.1% acetic acid solution. These solutions were injected subcutaneously (sc), at a volume of 1.0 mL/kg body weight.

2.2. Animals

The experiment was conducted with 32 male Wistar rats weighing between 160 and 180 g at the start of the experiments. Groups of eight animals were kept in Plexiglas cages with free access to food and water in a room with controlled temperature (23 °C±1 °C) and on a 12 h-light/dark cycle with lights on at 7:00 a.m. The number of animals used was the minimum to obtain relevant results and they were maintained and used in accordance to the guidelines of the Brazilian Association for Laboratory Animal Science (COBEA), following international norms of care and animal maintenance. The rats were randomly assigned to four groups: sedentary-control (SC), sedentary-reserpine (SR), exercise-control (EC), exercise-reserpine (ER).

2.3. Training protocol and experimental procedure

All exercised rats were subjected to swimming exercise in a plastic container (depth 45 cm) under continuous supervision, with the water temperature set to 34 °C±1 °C, 1 h/day, 5 times per week during 11 weeks. The duration of swimming was initially 15 min and was gradually increased by 15 min/day until reach a maximal of 60 min that was maintained during all the training period. The masses of the weights, which were fixed at the back of the rats, were increased gradually during two weeks, until a maximal of 7% of rats body weight (Chaumont et al., 2001).

One day after the last training session, all the animals received an injection of vehicle (0.1% acetic solution) or reserpine solution (1 mg/kg body weight in 0.1% of acid acetic solution), subcutaneously, for 3 days every other day, totaling two injections. The animals' weight was recorded weekly during the experiment.

2.4. Training verification

Immediately after the behavioral evaluations (see Sections 2.5 and 2.6) all the rats were sacrificed by decapitation and the heart was removed and weighed. The heart weight (mg)/body weight (g) (HW/BW) ratio was used as an index of cardiac hypertrophy (Tharp and Carson, 1975).

2.5. Behavioral testing

On the fourth day (between 22 and 24 h after the last reserpine or vehicle injection), all the rats were observed for the quantification of orofacial dyskinesia (OD): The animals were placed individually in cages (20×20×19 cm) containing mirrors under the floor 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) frequency and the duration of facial twitching (FT) was recorded during 5 min after a period of 2 min adaptation (hand operated counters were employed). Observers were blind to the drug treatments.

The behavioral experiments were conducted between 09:00 and 11:00 a.m.

2.6. Tissue preparation and oxidative stress parameters

Immediately after the behavioral evaluation (between 26 and 28 h after the last reserpine or vehicle injection), the rats were decapitated; the brains were removed and put on ice, 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 at 3000 ×*g* for 10 min and the supernatants were used for lipid peroxidation and catalase activity. Lipid peroxidation was determined by measuring accumulation of thiobarbituric acid reactive substances (TBARS) as described by Ohkawa et al. (1979). Catalase was quantified by measuring the disappearance of H_2O_2 at 240 nm (Aebi et al., 1995).

2.7. Statistical analysis

All the data were analyzed by a two-way ANOVA (2 (sedentary/exercise)×2 (control/reserpine)) followed by Duncan's multiple range test, when appropriated (Siegel, 1956).

3. Results

Verification of training program: Heart weight (mg), final body weight (g), heart weight/body weight ratios (heart hypertrophy index) are shown in Table 1. Two way ANOVA revealed a significant main effect of intense exercise on heart weight [$F(1,20)=56.90$, $P<0.001$] and heart weight/body weight ratios [$F(1,20)=57.21$, $P<0.001$]. Univariate ANOVA followed by Duncan's multiple range test revealed that exercised groups (EC and ER) showed increase of

Table 1
Mean values of heart weight, final body weight and heart weight/body weight ratios for sedentary (S) and exercised (E) rats, treated with vehicle or reserpine (C and R, respectively)

Group	Heart weight (mg)	Final body weight (g)	Ratio (mg/g)
SC	972.80±43.0	367.8±5.8	2.64±0.10
SR	1027.63±10.6	388.0±4.5	2.65±0.10
EC	1281.10±26.7*	378.5±6.8	3.38±0.10*
ER	1247.30±47.1*#	374.5±7.8	3.33±0.09*#

Data (mean±S.E.M.), ($n=8$) were analyzed by two-way ANOVA followed by Duncan's test. *($P<0.001$) difference from sedentary-control group (SC); #($P<0.001$) difference from sedentary-reserpine group (SR).

heart weight and of heart hypertrophy (organ-to-body weight ratio), when compared with sedentary groups (SC and SR), indicating the effectiveness of the exercise protocol. Body weight was not modified by physical training or reserpine administration.

Orofacial movements: The effects of reserpine treatment on orofacial movements in rats are shown in Fig. 1. Two way ANOVA revealed a significant main effect of reserpine [$F(1,28)=178.31$; $P<0.001$] and a significant reserpine × exercise interaction [$F(2,28)=6.92$; $P<0.05$] for VCM frequency (Fig. 1A). Univariate ANOVA followed by Duncan's multiple range test revealed that sedentary and exercised rats treated with reserpine (SR and ER) displayed an increase in VCM when compared to control groups (SC and EC). In fact, ER group showed VCM frequency significantly higher than that of both reserpine-treated sedentary (SR) and vehicle-treated (EC) exercised rats.

For duration of FT, two way ANOVA yielded a significant main effect of reserpine [$F(1,28)=272.68$; $P<0.001$] (Fig. 1B). Univariate analysis, followed by Duncan's multiple range test, revealed that sedentary and exercised rats treated with reserpine (SR and ER) displayed an increase in FT duration when compared to control group (SC). In fact, the duration of FT of reserpine-treated exercised rats (ER) was significantly higher than that of -exercised rats (EC), and similar to reserpine-treated sedentary group (SR).

3.1. Biochemical analysis

The results of intense exercise and reserpine treatment on TBARS levels and catalase activity in brain striatum are shown in Fig. 2. Two way ANOVA of TBARS levels revealed a significant main effect of exercise [$F(1,28)=132.54$; $P<0.001$], reserpine treatment [$F(1,28)=142.47$; $P<0.001$] and exercise × reserpine interaction [$F(2,28)=37.10$; $P<0.001$) (Fig. 2A). Post hoc comparisons by Duncan's multiple range test indicated a significant increase on TBARS levels in ER group when compared to the other groups. The reserpine administration (SR) and the exercise (EC) caused *per se* a significant increase in TBARS levels, when compared to control group (SC).

Two way ANOVA revealed a significant main effect of exercise and reserpine on striatal catalase activity, [$F(1,28)=4.32$, $P<0.046$] and [$F(1,28)=39.68$, $P<0.001$] respectively, (Fig. 2B). Univariate ANOVA followed by Duncan's multiple range test revealed that sedentary and exercised rats treated with reserpine showed a significant increase of catalase activity when compared to the control group (SC). In fact, ER group showed catalase activity significantly higher than that of reserpine-treated sedentary (SR) and vehicle-treated (EC) exercised rats.

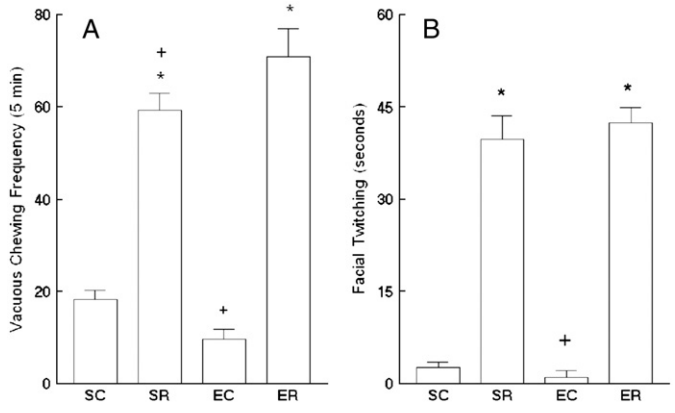

Fig. 1. Effects of reserpine administration (1.0 mg/kg sc every other day, for 3 days) (SR) or vehicle (SC) on sedentary rats ($n=16$) and rats submitted to intense exercise ($n=16$) (ER) or (EC) on vacuous chewing frequency (A) and facial twitching duration (B). Data (mean ± S.E.M.) were analyzed by two-way analysis of variance followed by Duncan's test. *Indicates a significant difference from SC group for $P<0.001$, $^{+}$indicates a significant difference from ER group for $P<0.001$.

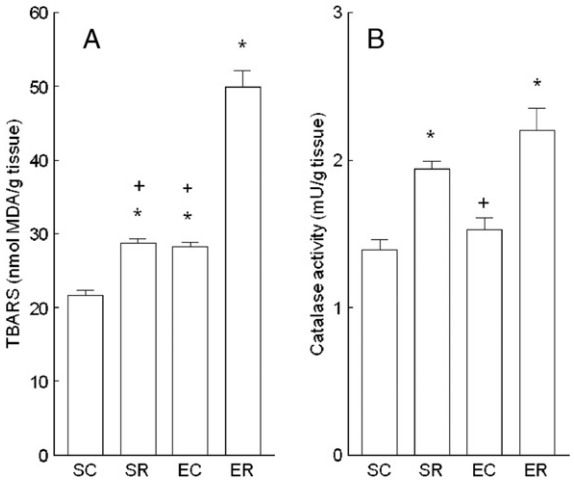

Fig. 2. Effects of reserpine administration (1.0 mg/kg sc every other day, for 3 days) (SR) or vehicle (SC) on sedentary rats ($n=16$) and rats submitted to intense exercise ($n=16$) (ER) or (EC) on TBARS levels (A) and catalase activity (B) in the striatum. Data (mean ± S.E.M.) were analyzed by two-way analysis of variance followed by Duncan's test. *Indicates a significant difference from SC group for $P<0.05$, $^{+}$indicates a significant difference from ER group for $P<0.001$.

4. Discussion

Recently we have showed the beneficial effects of chronic physical exercise (moderate intensity) in an OS animal model, suggesting beneficial effects in neurological diseases associated with orofacial movements (Teixeira et al., 2008). Here we have studied a gradual increasing in the exercise intensity because variations in the frequency and content of the physical exercise can have an influence on brain functions, leading to various disturbances, which can be measured by behavioral, biochemical and genetic modifications (Kleim et al., 2003; Sarbadhikari, 1995). Interestingly and similar to other researchers, we did not observe variation in the body weight of the exercised animals compared to the controls at the end of the experiment (Gündüz et al., 2004; Radak et al., 2001). The reasons for the absence of an effect of exercise on final body weight remains unknown, but it can be related to change in the proportion of muscular and fat tissue in the sedentary and trained groups.

The primary factor involved in reserpine-induced vacuous chewing behaviour is related to dopamine depletion and reduced activation of D_2 receptors (Neisewander et al., 1991, 1994) In line with this, literature data have indicated that dopamine plays an important role in motor activation (Freed and Yamamoto, 1985) and an increase in dopamine metabolism was observed in several brain regions of rats during physical activity (Meeusen and De Meirleir, 1995). Of particular interest for the animal model chosen here, literature data have indicated the participation of an elevation in dopamine metabolism with orofacial movement disorders in reserpine-induced animal models and in human diseases (Abílio et al., 2003a; Burger et al., 2003; Cadet and Kahler, 1994; Faria et al., 2005; Naidu et al., 2003; Raghavendra et al., 2001; Sagara, 1998; Singh et al., 2003; Sussman et al., 1997). In this sense, the reserpine is an OS inductor, mainly by preventing the storage of dopamine (DA) in neuronal vesicles via inhibition of the vesicular monoamine transporter (VMAT). This causes an increase in the catabolism of cytosolic DA (by Monoamine oxidase), which can contribute to accelerate the mechanism(s) leading to OS (Abílio et al., 2003a; Bilzka et al., 2007; Burger et al., 2003; Naidu et al., 2004). In line with this, this monoamine depletor reduces the uptake of DA, increasing its availability in the cytosol of dopaminergic neurons. This cytosolic DA can be oxidized to *O*-quinone aminochrome

stimulating one of the major sources of reactive species involved in the degenerative processes (Paris et al., 2001, 2005; Segura-Aguilar et al.; 2002).

In our previous study, we have demonstrated that moderate chronic exercise displayed a beneficial effect by partially preventing the increase in FT induced by reserpine (Teixeira et al., 2008). Here, in contrast, we observed that the reserpine treatment increased VCM and FT and that gradual intense physical activity did not alter these parameters. Exercise and reserpine treatments increased TBARS when compared to control group in striatal tissue. In fact, the gradual increase in the intensity of exercise was not enough to prevent the development of lipid peroxidation in the striatal region, which was more evident when in association with reserpine (OS inductor). Together, these results shown that the effects of intense exercise and reserpine treatment may result in an increase of dopamine metabolism. In fact, the pro-oxidant effect of the association of reserpine with exercise was observed by the increase of TBARS levels and catalase activity. The development of OD may be related to this striatal oxidative damage, which is in line with the view of literature data showing that catalase activity exerts a critical role in the development of OD and OS (Abílio et al., 2004; Faria et al., 2005). Similarly, Margonis et al. (2007) have explained an increase of catalase activity by a compensatory mechanism involved in the scavenging of free radicals after exercise.

Recently, Acikgoz et al. (2006) showed that acute exhaustive exercise did not change antioxidant defenses in frontal cortex and striatum, suggesting that exercise does not induce significant OS, and their results are not contradictory to those presented here because our experimental paradigm was performed chronically. In line with this, different researchers have submitted rats to moderate chronic exercise and observed an increase of catalase activity in brain and other tissues, relating this effect to an increase of antioxidant defenses (Devi and Kiran, 2004; Gündüz et al., 2004; Liu et al., 2000; Somani et al., 1995). Here we have found that the intense exercise protocol associated to reserpine treatment caused an increase in striatal catalase activity. In this sense, the increase in catalase activity can be a compensatory mechanism involved in the detoxification of reactive species in dopaminergic brain regions that can be related to a higher consumption of oxygen after chronic intense exercise (Jenkins, 1988; Sjodin et al., 1990) and to a greater generation of dopamine-quinones by reserpine administration (Fuentes et al., 2007). Various researchers have determined the effects of exercise on the antioxidant defenses in different tissues, including in brain regions (Somani et al., 1995; Ogonovszky et al., 2005; Acikgoz et al., 2006). The results presented here demonstrate for the first time that chronic and gradual intense exercise can change OS and antioxidant defenses in striatum which can be involved in movement disorders. These findings may be particularly important in clinical situations, when the OS and the neurotoxicity are closely involved.

In conclusion, the results presented here indicated that, in general, gradual chronic intense exercise had pro-oxidant effect by itself (as assessed by TBARS in striatum). In addition, when it was associated with reserpine treatment, intense physical exercise caused further increase in striatal TBARS and orofacial dyskinesia (OD), suggesting that OS is an important factor in the development of OD.

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