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Performance-enhancing and thermoregulatory effects of intracerebroventricular dopamine in running rats

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ABSTRACT

To assess the role of central dopamine on metabolic rate, heat balance and running performance, 2.0 μL of 5×10^{-3} M dopamine solution (DA) or 0.15 M NaCl (SAL) was intracerebroventricularly injected in Wistar rats 1 min before running on a motor-driven treadmill, according to a graded exercise protocol, until fatigue. Oxygen consumption (VO_2) and body temperature (T_b) were recorded at rest, during exercise, and after 30 min of recovery. DA induced a marked increase in workload (~45%, $p<0.05$). At fatigue point, DA-injected rats attained ~29% higher maximum oxygen consumption (VO_{2max}) and ~0.75 °C higher T_b than SAL-injected rats. Despite the higher VO_{2max} and T_b attained during exercise, DA-treated rats reached VO_2 basal values within the same recovery period and dissipated heat ~33% faster than SAL-treated rats ($p<0.05$). The mechanical efficiency loss rate was ~40% lower in DA than in SAL-treated rats ($p<0.05$), however, the heat storage was ~35% higher in the DA group ($p<0.05$). Our results demonstrate that increased DA availability in the brain has a performance-enhancing effect, which is mediated by improvements in the tolerance to heat storage and increases in the metabolic rate induced by graded exercise. These data provide further evidence that central activation of dopaminergic pathways plays an important role in exercise performance.

1. Introduction

High body temperature (T_b) is considered to be a limiting factor during prolonged physical exercise (Caputa et al., 1986; Fuller et al., 1998; González-Alonso et al., 1999; Jessen, 1987; Nielsen et al., 1993). It is also associated with a reduction in the central nervous system (CNS) drive for exercise (Nielsen et al., 1990; Nielsen et al., 1997; Walters et al., 2000), which leads to the termination of work (fatigue) in animals (Fuller et al., 1998) and healthy humans (González-Alonso et al., 1999; MacDougall et al., 1974). The hypothesis that sublethal hyperthermia precipitates feelings of fatigue, and thus establishes a safeguard against heat stroke by protecting the brain from thermal damage, is supported by various studies (Caputa et al., 1986; Cheung, 2007; Jessen, 1987; Nybo, 2008; Walters et al., 2000). Therefore, considering that fatigue is coincident with, or may be precipitated by, high T_b and/or heat storage, the activation of a central mechanism that increases heat loss and prevents hyperthermia could improve exercise performance.

It has been demonstrated that dopamine (DA) and DA agonists acting in the brain exert thermoregulatory effects characterized by a decrease in body metabolism and in T_b, and also by regulated hypothermia (anapyrexia) (Barros et al., 2004; Chaperon et al., 2003; Steiner and Branco, 2002; Gurrera, 1999; Nunes et al., 1991; Oerther, 2000; Varty and Higgins, 1998). Since increased heat dissipation may be neuroprotective, the activation of central dopaminergic systems could influence exercise performance. In fact, acute inhibition of DA reuptake by bupropion treatment improves exercise performance in humans and rats in a warm environment (Hasegawa et al., 2005b; Watson et al., 2005). Recently, it was shown that changes in T_b in running rats after bupropion administration were accompanied by an increase in the extracellular concentration of DA in the preoptic area of the anterior hypothalamus, an important locus for thermoregulation. This increase was also accompanied by an improvement in running performance (Hasegawa et al., 2008). These results indicated that DA neurotransmission might be involved in exercise performance by dampening or overriding inhibitory signals arising from the CNS to cease exercise due to hyperthermia.

DA influences other physiological responses and mechanisms that could similarly modify running performance, such as arousal, reward, motivation (Benaliouad et al., 2007; Bressan and Crippa, 2005; Drew et al., 2007; Meeusen, 2005), sympathetic nervous system activity (Arnerić et al., 1984; Gurrera, 1999), stress response (LeBlanc and Ducharme, 2007; Mannelli et al., 1997, 1999), and motor control (Di Stefano et al., 2008). Taking into account that central DA metabolism is enhanced during exercise in animals (Nybo and Secher, 2004), and that central DA depletion has been linked to CNS fatigue (Chaouloff, 1989; Davis and Bailey, 1997; Davis, 2000), the aim of the current study is to assess the effects of central administration of DA on heat balance, energetic cost, and running performance in rats submitted to

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graded exercise until fatigued. In addition, we measure the concentration of DA and its metabolite dihydroxyphenylacetic acid (DOPAC) in brain areas surrounding the cerebral ventricular system, such as the hypothalamus, the preoptic area, and the hippocampus.

2. Materials and methods

2.1. Ethics statement

All experiments were approved by the Ethics Committee for the Care and Use of Laboratory Animals of the Federal University of Minas Gerais, and were carried out in accordance with the regulations described in the Committee's Guiding Principles Manual (protocol 057/05).

2.2. Animals

Male Wistar rats (250–300 g) were housed individually at a room temperature of 22 ± 2 °C under 14 h light:10 h dark light regime (on 6 am/off 8 pm) and had free access to water and rat chow. Following anesthesia with a mixture of ketamine (2.0 mg/kg body weight; ip) and xylazine (2.0 mg/kg body weight; ip), the rats were fixed to a stereotaxic apparatus (David Kopf Instruments, M-900, Tujunga, CA, USA), and a guide cannula (22 G) was implanted into the right lateral cerebral ventricle using a previously described technique (Rodrigues et al., 2004; Soares et al., 2004). During the same surgical procedure, a TR3000 VM-FH temperature sensor (Mini Mitter, Sun River, OR) was implanted into the peritoneal cavity through a small incision in the linea alba. Following the surgical procedure, the rats received a single dose of analgesic (Flunixin 0.11 mg/100 g body weight; im) and antibiotic mixture (Pentabiótico®—for small animals, Fort Dogde, Brazil, 0.2 mL; im). All animals were allowed to recover for at least 1 week before being submitted to the test exercise protocol. The rats were first familiarized with the metabolic motor-driven treadmill by running 5 min per day at 5% inclination for five consecutive days. The speed was 10 m min^{-1} on the first and second days and it increased to 11, 13 and 15 m min^{-1} on subsequent days. The other purpose of this preliminary exercise was to show the rats which direction to run. All experiments were performed at a room temperature of 22 ± 1 °C and between 01:00 p.m. and 05:00 p.m.

2.3. Exercise

Graded exercise was performed on a metabolic motor-driven treadmill (Columbus Instruments, OH, USA) at a constant inclination of 5%. The rats started running at 10 m min^{-1}, and treadmill speed was increased by 1 m min^{-1} every 3 min until fatigue. Fatigue was defined as the point at which the animals were no longer able to keep pace with the treadmill (Rodrigues et al., 2004; Soares et al., 2004). Time to fatigue (minutes) and workload (kgm) were considered indices of running performance.

2.4. Experimental protocol

On the day of the experiment, the animals were allowed to rest for 1 h on the treadmill before being submitted to the test. A needle (30 G) protruding 0.3 mm from the tip of the guide cannula was introduced into the right lateral cerebral ventricle by connecting it to a Hamilton syringe. One minute prior to exercise, 2.0 µL of 0.15 M NaCl (SAL) or 2.0 µL of 5×10^{-3} M (10 nmol total) DA hydrochloride (Sigma-Aldrich, DA) solution was injected into the right lateral ventricle. Rats were randomly assigned to groups receiving either SAL or DA solution. An interval of at least three days was allowed for the animals to recover between the treatments. Additional control experiments were carried out in resting rats. Control animals were submitted to similar experimental procedures, but instead of exercising, they were allowed to move freely on the turndown treadmill during 60 min (habituation period) and also for additional 30 min after the injection procedure.

T_b was measured by telemetry (Mini Mitter, Sun River, OR). Oxygen consumption (VO_2) was measured by open-flow indirect calorimeter (Columbus Instruments), which was calibrated before each use with a certified mixture of gases (20.5% O_2 and 0.5% CO_2). VO_2 (mL O_2 kg^{-1} min^{-1}) and T_b (°C) were continuously recorded on-line by a computerized system (Oxymax Apparatus, Columbus Instruments for VO_2 and Mini Mitter, Sun River, OR for T_b registrations). T_b and VO_2 were recorded at rest, during exercise until fatigue and during a 30 min of recovery.

2.5. Calculations

Body heating rate (BHR; °C min^{-1}), the rate of increase in T_b, was calculated as BHR = ΔT_b / (running time interval), where ΔT_b represents the change in T_b($T_f - T_i$) and T_f and T_i represent T_b at the fatigue point and prior to exercise, respectively. Heat storage was calculated (Gordon, 1993) as HS = (ΔT_b) · $m \cdot c$, where m represents body weight in grams and c represents specific heat of the body tissues (0.826 cal g^{-1} $°C^{-1}$). Heat loss rate (HLR, °C min^{-1}), the rate of decrease in T_b during the recovery period, was calculated as HLR = ΔT_b / (recovery time interval), where ΔT_b represents the change in T_b($T_i - T_f$) and T_i and T_f represent T_b at the fatigue point and at 30 min after the fatigue point, respectively. Workload (k gm) was calculated as: [body weight (kg)] · [time to fatigue] · [treadmill speed (m min^{-1})] · [sin θ (treadmill inclination)] (Brooks and White, 1978; Brooks et al., 1984; Lima et al., 1998). Mechanical efficiency (ME; %) was calculated in two phases of graded exercise intensity: 0–40% of VO_2 max. and 60–100% of VO_2 max. by the formula: ME = (Workload / energetic cost) · 100 (Brooks et al., 1984; Lacerda et al., 2006; Soares et al., 2003).

2.6. DA and DOPAC measurements

The rats received the intracerebroventricular guide cannula implant as described above. Immediately before exercise or after a resting period of 60 min, SAL was injected into the right lateral cerebral ventricle. Continuous exercise was performed at an intensity of 20 m $min-^{1}$ and 5% inclination, which corresponded to an oxygen uptake of 70% of VO_{2max}. Rats were randomly assigned to three groups: 1. running for 20 min; 2. exercising until fatigue; 3. carried out in resting period of 60 min. As soon as one of these targets were reached, the animals were killed by decapitation. The brain was quickly removed and washed with ice-cold saline. The hypothalamus, preoptic area, and hippocampus were rapidly dissected out on an ice-cold plate and immediately frozen in dry ice and stored at −80 °C. Samples remained at −80 °C until DA and its metabolite dihydroxyphenylacetic acid (DOPAC) were measured by high-pressure liquid chromatography (HPLC). The HPLC system was equipped with a reverse-phase column (Shim Pack CLC-OSD; 25 cm, 5 µm, Shimadzu). The potential was set at 850 mV versus an Ag/AgCl reference electrode. A mobile phase containing 31.4 g citric acid, 584 mg NaCl, 800 mL milliQ water, 140 mg octylsodium sulfate, 48 mL acetylnitrile and 28 mL tetrahydrofurane (pH 3.0) was filtered and pumped through the system at a flow rate of 1.0 mLmin^{-1}. The brain tissues were weighed and homogenized in perchloric acid (0.1 M) and centrifuged at 15,300 × g for 20 min at 6 °C. The supernatants were then filtered through a Millipore membrane (0.22 µ pore size; 13 mm; Millex,SP, Brazil). Twenty microliters were injected into the HPLC-EC system for analysis (Shimadzu, Kyoto, Japan). Quantification of DA and DOPAC was made by comparing the peak area to a standard curve.

2.7. Statistical analysis

The data are reported as means ± standard error means (S.E.M.). Differences between groups and the effect of time were evaluated using the two-way ANOVA followed by the Newman-Keuls test. The

Table 1
Effect of intracerebroventricular injection of 2 µL of dopamine solution [5×10^{-3} M] (DA) or 2 µL of [0.15 M] NaCl (SAL) on changes in oxygen consumption (VO_2) and body temperature (T_b) in freely moving rats at rest.

	VO_2 (mL kg^{-1} min^{-1})		T_b (°C)	
Time (min)	SAL	DA	SAL	DA
Basal	18.15 ± 0.72		37.74 ± 0.22	
1	+ 0.55 ± 0.33	− 1.24 ± 0.17[a]	+ 0.08 ± 0.01	− 0.17 ± 0.07[a]
3	+ 0.86 ± 0.26	− 1.71 ± 0.16[a]	+ 0.06 ± 0.02	− 0.18 ± 0.04[a]
5	+ 2.38 ± 0.56	− 0.56 ± 0.30[a]	+ 0.04 ± 0.03	− 0.18 ± 0.05[a]
10	+ 4.30 ± 0.96	− 0.69 ± 0.64[a]	+ 0.01 ± 0.04	− 0.19 ± 0.03[a]
15	+ 4.23 ± 1.22	− 0.74 ± 0.67[a]	+ 0.01 ± 0.06	− 0.26 ± 0.02[a]
20	+ 3.08 ± 1.88	− 0.51 ± 0.93	+ 0.03 ± 0.04	− 0.30 ± 0.04[a]
25	+ 1.36 ± 1.94	− 0.86 ± 0.89	+ 0.04 ± 0.05	− 0.27 ± 0.05[a]
30	+ 1.00 ± 1.51	− 0.99 ± 0.93	+ 0.05 ± 0.07	− 0.39 ± 0.17

Values are expressed as mean ± S.E.M. $n = 6$/group.
[a] $p<0.05$ compared to SAL.

data were also compared using paired or unpaired Student's *t*-tests, as applicable; significance level was set at $p<0.05$.

3. Results

Table 1 shows changes in VO_2 and T_b induced by intracerebroventricular injections of DA and SAL in freely moving rats at rest. DA injection induced a small but persistent decrease in both measured parameters, VO_2 and T_b. However, the effect of DA injection in T_b was longer (25 min) than in VO_2 (15 min).

As illustrated in Fig. 1A, in DA-treated rats ($n = 6$ rats), there was a marked enhancement in running performance, measured as a significant increase in time to fatigue (27 ± 5 min, DA, vs. 17 ± 3 min, SAL, $p<0.05$) and in the workload performed (10.7 ± 2.5 kgm, DA, vs. 5.9 ± 1.3 kgm, SAL, $p<0.05$). These rats also reached higher exercise intensities compared to SAL-treated rats (SAL treatment, $n = 6$ rats).

Graded exercise induced a gradual increase in VO_2 in both treatment groups (DA and SAL). A difference from baseline could already be observed after the first three minutes of exercise, with both treatments showing a similar time course. The maximum metabolic rate (VO_{2max}) was attained at fatigue point for both treatments (Fig. 1A). However, DA-treated rats fatigued ~10 min later than SAL-treated rats ($p<0.05$; Figs. 1A and 2A), with VO_{2max} ~30% greater than for SAL treatment ($p<0.05$). Despite the greater VO_{2max} attained by the DA-treated rats, the metabolic rates of both treatment groups returned to basal values after a 30-minute recovery period (Fig. 1B).

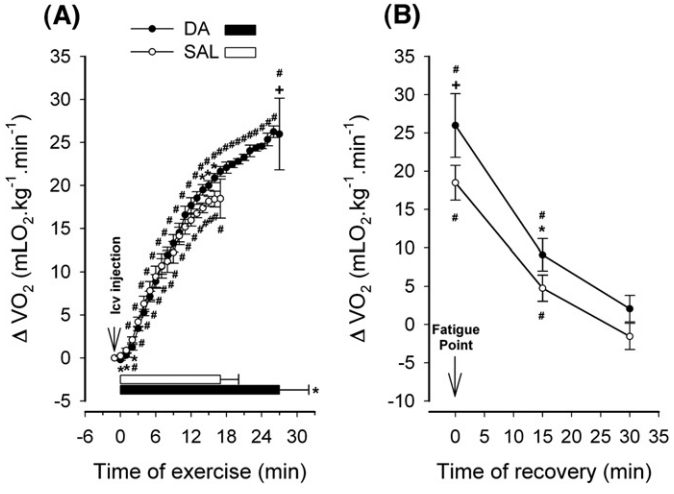

Fig. 1. Effect of intracerebroventricular injection of 2 µL of dopamine solution [5×10^{-3} M] (DA) or 2 µL of [0.15 M] NaCl (SAL) on changes in oxygen consumption (ΔVO_2) of rats during (A) exercise and (B) recovery period. Horizontal bars represent time to fatigue. Data are expressed as mean ± S.E.M., $n = 6$ in each treatment. *$p<0.05$ compared with SAL fatigue point; +$p<0.05$ compared with SAL; #$p<0.05$ compared with corresponding basal value (Basal VO_2: 18.21 ± 0.94 mL kg^{-1} min^{-1}).

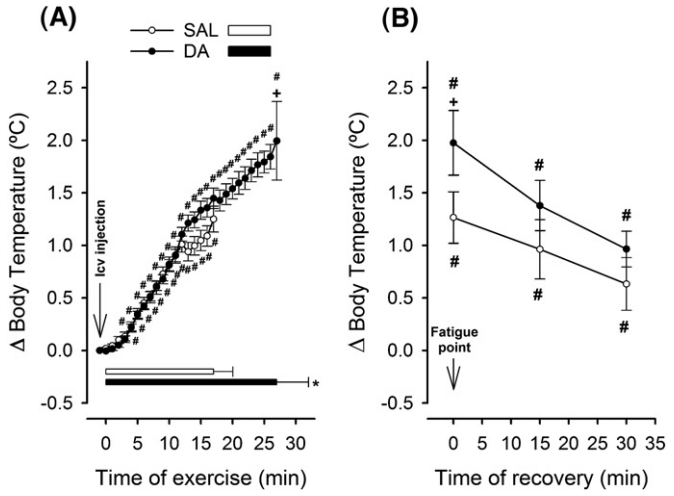

Fig. 2. Effect of intracerebroventricular injection of 2 µL of dopamine solution [5×10^{-3} M] (DA) or 2 µL of [0.15 M] NaCl (SAL) on changes in body temperature (ΔT_b) of rats during (A) exercise and (B) recovery period. Horizontal bars represent time to fatigue. Data are expressed as mean ± S.E.M., $n = 6$ in each treatment. *$p<0.05$ compared with SAL fatigue point; +$p<0.05$ compared with SAL; #p<0.05 compared with corresponding basal value (Basal T_b: 37.74 ± 0.22 °C).

Exercise also induced a similar gradual rise in T_b in both treatment groups (DA and SAL). However, at the fatigue point, T_b was ~0.75 °C greater in the DA-treated rats than in the SAL-treated rats ($p<0.05$) (Fig. 2A). After a 30-minute recovery period, T_b in both treatment groups had not yet returned to basal values (Fig. 2B), although DA-treated rats dissipated heat ~33% faster than SAL-treated rats ($p<0.05$). This difference was higher during the first 15 min of the recovery period (Fig. 2).

During the graded exercise, there were no differences in BHR between treatment groups; nevertheless, HS values were greater in DA- than SAL-treated rats. This difference was due to the longer time to fatigue observed in DA-treated animals (520 ± 93 cal, DA, *vs.* 336 ± 35 cal, SAL, $p<0.05$) (Fig. 3).

Mechanical efficiency values were similar between treatment groups during both phases of exercise (ME at 0–40%: 19.3 ± 4.0%, DA *vs.* 20.2 ± 3.9%, SAL; ME at 60–100%: 7.6 ± 1.4%, DA *vs.* 9.1 ± 1.4%, SAL). However, the mechanical efficiency loss rate was ~40% lower in the DA treatment group (0.23 ± 0.05% min^{-1}, DA, *vs.* 0.40 ± 0.09 % min^{-1}, SAL, $p<0.05$).

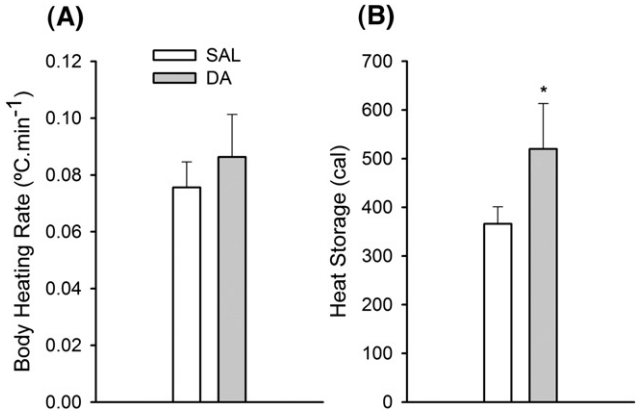

Fig. 3. Effect of intracerebroventricular injection of 2 µL of dopamine solution [5×10^{-3} M] (DA) or 2 µL of [0.15 M] NaCl (SAL) on (A) body heat rate (BHR) and (B) on heat storage (HS) of rats submitted to a graded exercise protocol. Data are expressed as mean ± S.E.M., $n = 6$ in each treatment. *p<0.05 compared with SAL.

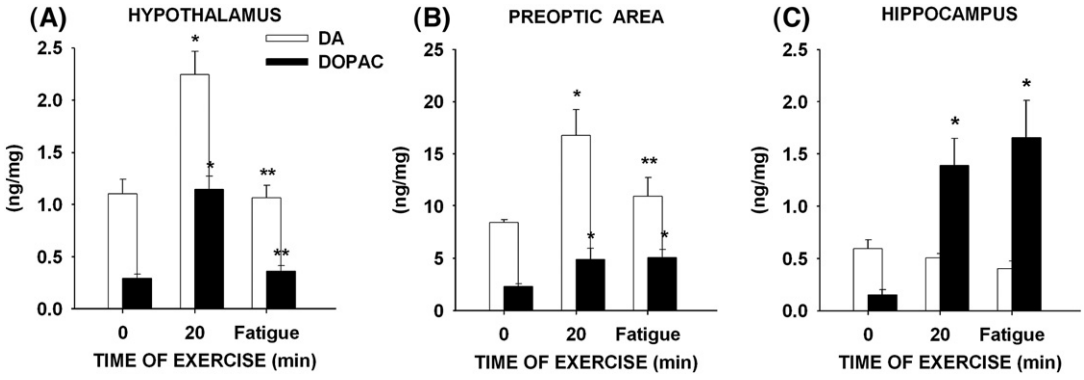

Fig. 4. Concentrations of dopamine (DA) and dihydroxyphenylacetic acid (DOPAC) in (A) hypothalamus, (B) preoptic area, and (C) hippocampus of resting and running rats for 20 min or until fatigue (20 m min^{-1}.5% inclination). $^{*}p<0.01$ compared to resting; $^{**}p<0.01$ compared to 20 min exercised rats.

Fig. 4 shows DA and DOPAC content in the studied brain areas. After 20 min of exercise, DA and DOPAC content in the hypothalamus doubled and tripled, respectively, compared to the rested group (Fig. 4A). On the other hand, following exercise until fatigue, the levels of DA and DOPAC returned to resting values (Fig. 4A). Similarly, after 20 min of exercise, there was a significant increase in the content of DA and DOPAC in the preoptic area (Fig. 4B). Following exercise until fatigue, the levels of DA returned to resting values, while DOPAC levels remained increased compared to the resting group (Fig. 4B). DA content within the hippocampus remained unchanged after 20 min of exercise and in fatigued-exercise rats (Fig. 4C). In contrast, after 20 min of exercise and in fatigued-exercise rats, the concentration of DOPAC in the hippocampus increased significantly in comparison with controls (Fig. 4C).

4. Discussion

The main finding of the present study was that an acute intracerebroventricular injection of DA improves exercise performance despite high heat storage and T_b at fatigue point. Moreover, it provides new evidence that DA transmission may increase heat storage and tolerance to hyperthermia by limiting or overriding inhibitory signals arising from the CNS to cease exercise due to hyperthermia. Furthermore, DA treatment improved heat dissipation rate during the recovery period. However, T_b at fatigue point was markedly higher in DA-treated animals (~40 °C). Therefore, our data suggest that central DA-mediated pathways are involved not only in thermoregulatory heat loss, but also in the ability of CNS neurons to detect and prevent thermal damage to the brain caused by high T_b. These results serve as further evidence for a role of the central dopaminergic system in thermoregulatory adjustment during exercise.

The association between hyperthermia and reduced physical performance has been shown in many mammalian species, including rodents (Fuller et al., 1998; Nielsen et al., 1993, 1997; Walters et al., 2000). The present study supports this association by showing that central DA can lead to reductions in metabolic rate and an increase in heat loss, reducing T_b and consequently improving running performance. Furthermore, our data agree with previous experiments (Hasegawa et al., 2005b, 2008; Watson et al., 2005) showing that central DA has an ergogenic effect on physical performance. Specifically, or data show that central DA leas to an improvement in running time and a reduction in the rate of mechanical efficiency loss during graded exercise.

The exact central pathways involved in the effects of intracerebroventricular injection of DA remain to be identified. Following intracerebroventricular injection, DA could have diffused to many brain structures, influencing a variety of physiological functions, including thermoregulation and metabolic control. In this context, the microinjected DA could have reached periventricular areas, such as the preoptic area within the anterior hypothalamus. Various studies point to preoptic area as a locus of T_b regulation (Ishiwata et al., 2002; Nagashima, 2006; Nagashima et al., 2000; Romanovsky, 2007; Zhang et al., 1997). It has been established that the preoptic area is an integrative region for the maintenance of metabolic (Coimbra and Migliorini, 1986, 1988; Santos et al., 1990, 1991), vasomotor, and thermal homeostasis in resting conditions, as well as during exercise (Hasegawa et al., 2005a). Furthermore, recent studies have indicated that increased DA content in the preoptic area may influence performance and increase total exercise time (i.e., ergogenic effect) (Hasegawa et al., 2008; Watson et al., 2005). As mentioned, since the ergogenic effect depends on thermoregulation, the hypothalamic preoptic area could be the brain area in which DA exerts its thermoregulatory actions, modulating heat production and dissipation during exercise, thus affecting running performance. Our results showing that DA content in hypothalamus and preoptic area increases during exercise, returning to basal levels at the fatigue point further support this hypothesis. In addition, previous studies have shown that an acute injection of DA and the noradrenaline reuptake inhibitor bupropion improves exercise performance and induces an increase in internal temperature during exercise in a warm environment. These changes in temperature were accompanied by an increase in the extracellular concentrations of DA and noradrenaline in the preoptic area in exercising rats, measured *in vivo* via microdialysis (Hasegawa et al., 2008). The current results corroborate these previous observations, showing that increased DA content in the CNS enhances exercise performance associated with an increase in T_b.

Another possible locus for the effects of microinjected DA may be the dopaminergic reward circuits (Koob and Moal, 2008). DA acting on the mesolimbic reward system, could overrule inhibitory signals arising from the CNS that would normally compromise running performance (Tella et al., 1996), as suggested by previous studies (Gurrera, 1999; Watson et al., 2005). Therefore, in the present study, the enhanced running performance could also be due to an inhibitory effect of DA in perceived effort during graded exercise. This hypothesis does not, of course, exclude the possibility that other neurotransmitter pathways, such as noradrenergic transmission, could also be involved in the effects observed in the present study.

In summary, the present study demonstrates that intracerebroventricular injection of DA results in a performance-enhancing effect, evidenced as a marked increase in running performance, workload output and VO_{2max}, and reduction in the rate of mechanical efficiency loss during exercise. In addition, DA treatment increases tolerance to heat storage and to elevated metabolic rate during exercise, and improves metabolic rate recovery and heat loss in the post-exercise period. Finally, our results provide further evidence that central dopaminergic systems exert important control on metabolic rate, thermoregulation, and the CNS drive for exercise performance.

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