Pharmacological Reports
2010, 62, 54–61
ISSN 1734-1140

Effects of blockade of central dopamine D_1 and D_2 receptors on thermoregulation, metabolic rate and running performance

Cláudio H. Balthazar[1], Laura H. R. Leite[1], Roberta M. M. Ribeiro[2], Danusa D. Soares[2], Cândido C. Coimbra[1]

[1]Department of Physiology and Biophysics, Institute of Biological Sciences, Federal University of Minas Gerais, 31270-901, Belo Horizonte, Brazil

[2]Department of Physical Education, School of Physical Education, Physical Therapy and Occupational Therapy, Federal University of Minas Gerais, 31270-901, Belo Horizonte, Brazil

Correspondence: Cândido C. Coimbra, e-mail: coimbrac@icb.ufmg.br

Abstract:
To assess the effects of a blockade of central D_1- and D_2-dopaminergic receptors on metabolic rate, heat balance and running performance, 10 nmol (2 µl) of a solution of the D_1 antagonist SCH-23390 hydrochloride (SCH, n = 6), D_2 antagonist eticlopride hydrochloride (Eti, n = 6), or 2 µl of 0.15 M NaCl (SAL, n = 6) was injected intracerebroventricularly into Wistar rats before the animals began graded running until fatigue (starting at 10 m/min, increasing by 1 m/min increment every 3 min until fatigue, 5% inclination). Oxygen consumption and body temperature were recorded at rest, during exercise and following 30 min of recovery. Control experiments with injection of two doses (10 and 20 nmol/rat) of either SCH or Eti solution were carried out in resting rats as well. Body heating rate, heat storage, workload and mechanical efficiency were calculated. Although SCH and Eti treatments did not induce thermal effects in resting animals, they markedly reduced running performance (–83%, SCH; –59% Eti, $p < 0.05$) and decreased maximal oxygen uptake (–79%, SCH; –45%, Eti, $p < 0.05$) in running rats. In addition, these treatments induced a higher body heating rate and persistent hyperthermia during the recovery period. Our data demonstrate that the alteration in dopamine transmission induced by the central blockade of dopamine- D_1 and D_2 receptors impairs running performance by decreasing the tolerance to heat storage. This blockade also impairs the dissipation of exercise-induced heat and metabolic rate recovery during the post-exercise period. Our results provide evidence that central activation of either dopamine- D_1 or D_2 receptors is essential for heat balance and exercise performance.

Key words:
dopamine receptor, thermoregulation, SCH-23390, eticlopride, exercise, central fatigue

Abbreviations: Eti – eticlopride hydrochloride solution, SAL – NaCl solution, SCH – SCH-23390 hydrochloride solution, T_b – body temperature, VO_2 – oxygen consumption, VO_{2max} – maximal oxygen uptake

Introduction

The increase in body temperature (T_b) that occurs in response to continuous or graded exercise results

from an imbalance between metabolic heat production and heat dissipation [21, 51, 52]. T_b is considered to be a limiting factor during prolonged physical exercise [10, 20, 22, 29, 38], and a high level of body heat storage is associated with the termination of work in animals [19] and healthy humans [22]. Evidence suggests that there is a critical absolute value of T_b and/or heat storage that determines the point of fatigue [19], reducing the central nervous system drive for exercise performance [39, 50]. There is also a hypothesis that hyperthermia precipitates feelings of fatigue and reduces motivation at a sublethal threshold, providing a safeguard against heat stroke and protecting the brain against thermal damage [10, 29, 50]. Therefore, considering that fatigue may be precipitated by high core temperature and/or heat storage, the blockade of a central mechanism that leads to heat loss and/or heat tolerance should impair exercise performance.

Such mechanisms could be mediated by the dopaminergic (DAergic) system. Dopamine (DA) and DA-receptor agonists exert thermoregulatory effects, including hypothermia and anapyrexia [12, 40, 43]. In fact, depletion or reduction of central catecholamines has been linked to central fatigue and exhaustion during exercise [11, 16, 17]. Regional cerebral DA metabolism is enhanced during exercise in animals, and during strenuous exercise the arterial concentration of DA is increased [41].

In humans and rats, DA reuptake inhibitors have been used to evaluate the effects of DA on exercise performance. It was recently shown that acute treatment with bupropion (a dual DA/noradrenaline reuptake inhibitor) increased the time of exercise in a warm environment. It is important to point out that this increased running performance was accompanied by a rise in internal temperature that reached 40°C or even higher values [27, 51]. These results suggest that central DA could be related to the enhancement of physical performance and that activation of DAergic pathways in the hypothalamus could be a predictor of exercise tolerance in the heat [6]. Inhibition of noradrenaline and DA reuptake has already been demonstrated to suppress heat loss mechanisms and elevate brain temperature and body temperature in freely moving rats [26].

Taking into account the observation that DA antagonists decrease spontaneous locomotion, greatly attenuate behavioral activation [30] and interfere with thermoregulation [9] and metabolic rate [36], the aim of this study was to assess the effects of central administration of DA- D_1 (SCH-23390, SCH) and D_2 (eticlopride, Eti) receptor antagonists on heat balance, metabolic rate and running performance in untrained rats subjected to graded exercise until fatigue.

Materials and Methods

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).

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 cycles and had free access to water and rat chow. Following anesthesia with a mixture of ketamine (2 mg/kg body weight; *ip*) and xylazine (2 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 [1]. During the same surgical procedure, a TR3000 VM-FH temperature sensor (Mini Mitter, Sun River, OR, USA) 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; intramuscular, *im*) and antibiotic mixture (Pentabiótico® – for small animals, Fort Dogde, Brazil, 0.2 ml; *im*). All animals were allowed to recover for at least one week before undergoing the test exercise protocol. The rats were familiarized with exercise on the metabolic motor-driven treadmill by running 5 min per day on a 5% incline for five consecutive days prior to the experiments. The speed was set at 10 m × min^{-1} on the first and second days, and at 11, 13 and 15 m × min^{-1} on subsequent days. The purpose of this preliminary exercise was to show the rats in which direction to run. All experiments were performed at a room temperature of 22 ± 1°C, between 1:00 p.m. and 5:00 p.m.