Neuroscience Letters 590 (2015) 193–198

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

The dynamics of physical exercise-induced increases in thalamic and abdominal temperatures are modified by central cholinergic stimulation

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HIGHLIGHTS

- Physostigmine affects the dynamics of exercise-induced increases in temperature.
- Thalamic temperature increases more rapidly than abdominal temperature.
- Physostigmine delays the exercise-induced increase in thalamic temperature.
- Central cholinergic stimulation does not affect physical performance.
- Cholinoceptors likely modulate brain heat loss during exercise.

ARTICLE INFO

Article history:
Received 30 October 2014
Received in revised form 14 January 2015
Accepted 30 January 2015
Available online 2 February 2015

Keywords:
Fatigue
Hyperthermia
Physostigmine
Thalamus
Thermoregulation
Treadmill running

ABSTRACT

Evidence has shown that brain and abdominal (T_{abd}) temperatures are regulated by distinct physiological mechanisms. Thus, the present study examined whether central cholinergic stimulation would change the dynamics of exercise-induced increases in T_{abd} and thalamic temperature (T_{thal}), an index of brain temperature. Adult male Wistar rats were used in all of the experiments. Two guide cannulae were implanted in the rats, one in the thalamus and the other in the right lateral cerebral ventricle, to measure T_{thal} and to centrally inject a cholinergic agonist, respectively. Then, a temperature sensor was implanted in the abdominal cavity. On the day of the experiments, the rats received an intracerebroventricular injection of 2 μL of 10^{-2} M physostigmine (Phy) or a vehicle solution (Veh) and were subjected to treadmill running until volitional fatigue occurred. T_{thal} was measured using a thermistor connected to a multimeter, and T_{abd} was recorded by telemetry. Phy injection delayed the exercise-induced increases in T_{thal} (37.6 ± 0.2 °C Phy vs 38.7 ± 0.1 °C Veh at the 10th min of exercise) and in T_{abd}. Despite the delayed hyperthermia, Phy did not change the rats' physical performance. In addition, the more rapid exercise-induced increase in T_{thal} relative to T_{abd} in the rats treated with Veh was abolished by Phy. Collectively, our data indicate that central cholinergic stimulation affects the dynamics of exercise-induced increases in T_{thal} and T_{abd}. These results also provide evidence of the involvement of cholinoceptors in the modulation of brain heat loss during physical exercise.

1. Introduction

The increase in core body temperature, including the increase in brain temperature (T_{brain}), is a landmark response to physical exertion observed in virtually all exercising mammals. Even under temperate conditions (i.e., ambient temperatures ranging from 18 °C to 25 °C), the T_{brain} of running rats reaches levels above 39 °C [5,8,12]; this marked hyperthermia may reduce the central nervous system drive for exercise, thereby limiting prolonged physical performance [3,15]. Evidence suggests that the brain is more sensitive to temperature fluctuations than other body organs [2]. In fact, augmented T_{brain} levels increase the blood–brain barrier permeability and cause cell edema, ultimately threatening the integrity of the neural tissue [11].

The brain accounts for a significant percentage of the whole body metabolic rate and heat production. Metabolic-derived heat

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http://dx.doi.org/10.1016/j.neulet.2015.01.082
0304-3940/

is primarily removed from the brain via blood flow, as supported by the observation that the blood temperature in the jugular vein is higher than that in the carotid artery under conditions of both rest and physical exercise [16]. In contrast to other vascular beds (i.e., the vasculature of the skin and splanchnic regions) in which blood flow is primarily regulated by neural sympathetic activity, brain blood flow is primarily modulated by self-regulation mechanisms and local metabolic factors [17]. These differences in metabolic rate and blood flow regulation indicate the existence of distinct mechanisms that control thermal homeostasis in the brain compared with other regions of the body core.

We previously demonstrated that the intracerebroventricular (icv) injection of physostigmine (Phy), an acetylcholinesterase inhibitor, enhanced tail skin heat loss [19,20], thereby attenuating the running-induced increase in core temperature measured in either the abdomen [19] or the colon [21]. Interestingly, the thermoregulatory effects mediated by Phy were consequent to the activation of aortic and carotid baroafferents [20], indicating that the increased cutaneous heat loss was not a "pure" thermoregulatory reflex triggered by central cholinergic stimulation. Because baroreflex activation also modulates blood flow in the brain [14,24], icv Phy is also expected to interfere with T_{brain} regulation. However, the effects of Phy on brain thermal homeostasis are currently unknown.

Because distinct mechanisms modulate vasomotor tonus and, consequently, heat loss in the brain and abdomen, we hypothesized that icv Phy would differentially affect T_{brain} and abdominal temperature (T_{abd}). Thus, the present study sought to determine whether central cholinergic stimulation attenuates exercise-induced brain hyperthermia, as previously observed for abdominal hyperthermia. Moreover, T_{brain} and T_{abd} are not homogeneous and do not respond similarly to exercise [5] or to several arousing stimuli, such as light, sound, and tail-pinch [10]. Therefore, this study also investigated the effects of central cholinergic stimulation on the dynamics of exercise-induced increases in T_{brain} and T_{abd}.

2. Materials and methods

2.1. Animals

Adult male Wistar rats weighing 250–350 g were used in all of the experiments. The rats were housed in individual cages under controlled light (lights on from 0500 until 1900 h) and temperature (24 ± 1 °C) conditions with water and rat chow provided ad libitum. All experimental procedures were approved by the local ethics committee for the care and use of laboratory animals (protocol 133/11) and were performed in accordance with the regulations described in the Committee's Guiding Principles Manual.

2.2. Experimental design

To investigate the effects of central cholinergic stimulation on the increase in T_{brain} during treadmill running, chronic guide cannulae were implanted in the thalamus and right lateral cerebral ventricle of the rats to measure the thalamic temperature (T_{thal}) and to inject drugs into the brain, respectively. A temperature sensor was also implanted in the abdominal cavity. After recovering from these procedures, the rats were familiarized with treadmill running. On the day of the experiments, each animal received an icv injection of Phy or a vehicle solution (Veh) and was immediately subjected to constant-speed exercise on a treadmill until volitional fatigue occurred. T_{thal} and T_{abd} were measured as core body temperature indexes. The ambient temperature inside the treadmill chamber was controlled at 24 ± 1 °C. Each animal was subjected to two experimental trials with an interval of at least 2 days between the trials. All of the experiments were performed between 0700 and 1100 h, and the order of the trials was randomized and balanced.

After the two exercise trials, the rats were implanted with a polyethylene catheter for the measurement of pulsatile arterial pressure to determine the effectiveness of the central cholinergic stimulation. Previous reports indicate that icv Phy markedly increases mean arterial pressure (MAP) in rats [19,20].

2.3. Surgical procedures

The animals were anesthetized with intraperitoneal (i.p.) ketamine and xylazine (90 and 10.5 mg/kg body mass, respectively). Prior to the surgeries, the rats received an intramuscular prophylactic dose of antibiotics (veterinary pentabiotic, 48,000 IU/kg) and a subcutaneous injection of analgesic medication (flunixin meglumine, 1.1 mg/kg). Each animal was fixed in a stereotaxic apparatus, and a stainless steel guide cannula (21 gauge and 18.0 mm in length) was implanted in the thalamus according to the following stereotaxic coordinates: anteroposterior, 2.3 mm posterior to the bregma; mediolateral, 1.5 mm to the left from the midline; dorsoventral, 5.5 mm below the dura mater [18]. A second guide cannula was implanted in the right lateral cerebral ventricle according to a previously described technique [13]. Immediately after these cannulae were implanted in the brain, a temperature sensor (G2 E-Mitter series, Mini-Mitter) was implanted in the abdomen. A small incision was made in the linea alba of the rectus abdominis, the abdominal cavity was exposed, and the telemetry transmitter was inserted and subsequently fixed to the left lateral abdominal wall with sutures. After insertion, the abdominal muscle and skin were sutured in layers. The rats were given at least one week to recover from these surgical procedures.

To measure pulsatile arterial pressure, a polyethylene catheter (a PE-10 connected to a PE-50, Becton Dickinson) filled with heparin diluted in isotonic saline was inserted into the left common carotid artery. The free end of the PE-50 tubing was tunneled subcutaneously and exteriorized at the cervical dorsal area. The rats were given 2 days to recover from this surgical procedure.

2.4. Familiarization with exercise on a treadmill

Light electrical stimulation (0.5 mA) was applied to gradually encourage the rats to exercise on a treadmill designed for small animals (Modular Treadmill, Columbus Instruments). After resting for 5 min on the treadmill belt, the rats were required to run for 5 min at a constant speed of 18 m/min and an inclination of 5% [7]. This familiarization protocol was conducted across 5 consecutive days. The purpose of these preliminary exercise sessions was to show the animals the direction in which they should run and to minimize their exposure to the electrical stimuli during the experimental trials. Rats that were unable to run well (i.e., rats that were frequently exposed to the electrical stimulation at the end of the treadmill belt) during the familiarization sessions were excluded from the study.

2.5. Physical exercise trials

On the day that the experiments were conducted, each rat was weighed, and a thermistor (Negative Temperature Coefficient Catheter Sensor; Beta ThermCorp.) was inserted through the guide cannula into the thalamus. Next, a 30-gauge, 16.3 mm-long injection needle connected to a Hamilton syringe via PE tubing was introduced through the guide cannula into the cerebral ventricle. The rats were randomly assigned to receive an icv injection of 2 μL of Veh (10% ethanol in saline) or 10^{-2} M Phy (Eserine, Sigma Chemical). The thermistor insertion and the injection lasted 2 min; the animals were then subjected to constant-speed exercise