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Short communication

Central losartan administration increases cardiac workload during aerobic exercise

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ABSTRACT

To assess the effects of central administration of losartan, an antagonist of angiotensin II AT_1 receptors, on cardiovascular function during aerobic exercise, heart rate, systolic and diastolic arterial pressures and rate pressure product of *Wistar* rats were measured as cardiac workload indexes. The animals ran on a treadmill until fatigue after an intracerebroventricular injection of losartan or saline. Pulsatile arterial pressure was recorded by a catheter implanted into the ascending aorta, from which were derived cardiovascular parameters to estimate the cardiac workload. Total exercise time and exercise workload were determined as performance indexes. The rats showed a more intense increase in heart rate after 8 min of exercise and sustained until fatigue ($P < .05$). Furthermore, the rats injected with losartan had a higher increase of both systolic and diastolic arterial pressures as well as rate pressure product from approximately 6 min of exercise until fatigued ($P < .05$). In addition, a 22% reduction in exercise time was found in losartan-rats ($P < .01$). This ergolytic effect induced by losartan was strongly inversely correlated with rate-pressure product during aerobic exercise ($r = 0.78$, $P \leq .01$). The data shows that central administration of losartan augments the cardiac workload during aerobic exercise, which courses in parallel with the reduced exercise performance.

1. Introduction

The inherent increase in metabolic rate induced by exercise requires a higher blood flow to working muscles, in order to match the energetic demand for muscular contraction, as well as to cutaneous vessels, to meet the demand of body temperature regulation (Gonzalez-Alonso et al., 2008). These demands are sustained by integrated autonomic cardiovascular adjustments mediated by neural signals originating from the brain (central command) and feedback signals arising from the skeletal muscles (exercise pressor reflex) and the aorta and carotid arteries (arterial baroreceptor reflex) (Fadel and Raven, 2012; Williamson et al., 2006).The end result is a rapid and reversible reset of the arterial baroreflex with exercise, primarily through modulation of sympathetic tonus, to raise heart rate (HR) and cardiac contractility, and ultimately mean arterial pressure (MAP) (Dampney, 2017; Fadel and Raven, 2012; Potts, 2006). In addition, blood flow redistribution is selectively altered by means of vasoconstriction of the less metabolic active tissues and vasodilation of the contracting muscles and the skin (Leite et al., 2012; Morrison, 2001).

Angiotensin II is a neuropeptide with multiple actions in the brain, including well-defined cardiovascular effects. Indeed, is has been established that there is a local rennin-angiotensin system in the brain (Jackson et al., 2018). The general consensus is that central angiotensin II, interacting with AT_1 receptors, contribute to the increase in blood pressure and in cardiac output by acting as a potent sympathetic tonus enhancer (Stebbins and Symons, 1995; Warren et al., 2001). Evidences indicate that the ability of brain angiotensin II to increase blood pressure accounts for its reduction on the sensitivity of arterial baroreflex control of HR (Mousa et al., 2008; Negrao and Middlekauff, 2008). In contrast, a hypotensive effect induced by central angiotensin II through the brain ventricular routes has also been described, as indicated by findings that central AT_1 receptors blockade with losartan produces an increase in arterial pressure via α1-adrenoceptors stimulation (De Luca Junior et al., 1994; De Luca Jr. et al., 1996, 2000; Sugawara et al., 2002).

It is important to point out that cardiovascular and

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thermoregulatory systems interact in the regulation of cutaneous blood flow since changes in cardiac output and in blood flow redistribution directly interfere on skin vascular conductance (O'Leary et al., 1985; Pires et al., 2010). In this sense, we have already shown that intracerebroventricular infusion of losartan in running rats reduces exercise performance due to an intense hyperthermia triggered by increased heat production and reduced tail heat dissipation (Leite et al., 2006, 2007, 2010, 2013). Based on previous evidence that central angiotensin II AT_1 receptor blockade during exercise induces sympathetic activation precociously at a lower level of exercise intensity (Leite et al., 2009), the delay in tail skin vasodilationinduced by central AT_1 receptor blockade seems to be associated with enhanced sympathetic vasoconstrictor tone.

Cardiorespiratory capacity is closely related to the exercise performance of humans and other homeothermic animals. Cardiac limitations and dysfunctions on cardiovascular autonomic control of blood pressure dramatically decrease the performance in daily physical activities. Currently, a high percentage of people are affected by dysfunctions of the neural control of the cardiovascular system as a consequence of obesity and hypertension (Caron et al., 2017; Charkoudian and Rabbitts, 2009). Alterations in the central pathways, reflex mechanisms and cardiac sympathetic control of blood pressure explain, in part, the low physical performance of the individuals above mentioned (Moraes-Silva et al., 2010; Spranger et al., 2017). Therefore, it is important to understand the central mechanisms that modulate the autonomic pathways of control of the cardiovascular system during physical activities.

Besides the actions of central angiotensin II on thermoregulation and physical capacity, it is still not known how the cardiovascular system is regulated during exercise until fatigue after central angiotensinergic blockade, and whether such control supports the reduced duration of the exercise (Leite et al., 2013). Thus, the purpose of the present study was to investigate the interference of intracerebroventricular blockade of AT_1 receptors on cardiovascular function in running rats and if the decreased physical performance induced by central losartan is associated with the sympathetic-controlled heart rate and blood pressure responses to exercise. Specifically, we tested the hypothesis that central treatment with losartan prior to exercise until fatigue (1) exacerbates cardiac work by concomitantly increasing MAP and HR, and (2) these effects are in agreement with the limited physical performance due to thermal imbalance (Leite et al., 2013).

2. Material and methods

2.1. Animals

Adult male *Wistar* rats weighing 230–270 g were used in all experiments. Animals were housed individually at a room temperature of 22 ± 2 °C under 14-h light:10-h dark cycles, with water and rat chow provided ad libitum.

All experimental procedures were approved by the Ethics Committee of the Federal University of Minas Gerais for the Care and Use of Laboratory Animals and were carried out in accordance with the regulations described in the Committee's Guiding Principles Manual.

2.2. Exercise familiarization

The animals were acclimatized to exercise on the motor-driven treadmill (Modular Treadmill, serial number 96002-2, Columbus Instruments, OH, USA) by running at a speed of 15 m min^{-1} at 5% inclination for 5 min d^{-1} during four consecutive days before the experiments. This preliminary exercise did not constitute training. Its purpose was to teach the animals in which direction to run. Electrical stimulation was determined according to each animal's tolerability (Leite et al., 2007, 2009).

2.3. Surgical procedures

Following the last familiarization exercise session, under anesthesia with a mixture of ketamine (72 mg/kg body weight i.p.) and xylazine (8 mg/kg body weight i.p.), 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 (Antunes-Rodrigues and McCann, 1970).

After the implantation of guide cannula in the ventricular space, the rats were implanted with a catheter to measure pulsatile arterial pressure. The polyethylene catheter (PE-10 connected to a PE-50, Becton Dickinson, Franklin Lakes, NJ, USA) filled with heparin diluted in isotonic saline was inserted ascending aorta via left common carotid artery. The free end of the PE-50 tubing was tunneled subcutaneously and exteriorized at the cervical dorsal area (Pires et al., 2010). Immediately after surgery, the rats received an intramuscular prophylactic dose of antibiotics (Pentabiotic, 24,000 IU/kg body wt, Fort Dodge) and a subcutaneous injection of analgesic medication (Flunixin Meglumine, 1.1 mg/kg body wt, Schering-Plogh) (Pires et al., 2010). All animals were allowed to recover for at least one week before being submitted to the experiments (Leite et al., 2006).

2.4. Experimental protocol

On the day of the experiments, the arterial catheter was connected through a 30 cm length of PE-50 to a pressure transducer (Biopac Systems, Santa Barbara, CA,USA), coupled to an A/D Data Acquisition System (MP100, Biopac Systems). In addition, a Hamilton syringe was connected by PE-10 tubing to the brain cannulae for drugs injection, and then the rats were placed inside the treadmill.

The animals were allowed to rest for 1 h in the rodent treadmill chamber before being submitted to the test. Immediately prior to exercise, 2.0 μL of 0.15 M NaCl (saline, n = 6) or 2.0 μL of losartan (Merck Sharpe and Dohme, Campinas, Brazil; 60 nmol, n = 6) were injected into the right lateral ventricle. The dose of losartan was based on the results of our previous experiments (Leite et al., 2006). Rats were randomly assigned to groups receiving either saline or losartan solution. The researchers were blinded to the randomization scheme. An interval of at least two days was allowed for the animal to recover between the tests. Immediately after the intracerebroventricular injections, the animals were individually submitted to running exercise until fatigue. Exercise was performed between 10:00 and 14:00 h at a room temperature of 22 ± 2 °C. The intensity of exercise (18 m min^{-1} and 5% inclination) corresponded to an oxygen uptake of ~66% of maximal oxygen uptake, which represents a physical activity of moderate intensity (Leite et al., 2007, 2009). Fatigue was defined as the point at which the animals were no longer able to keep pace with the treadmill (Leite et al., 2006, 2010).

2.5. Measurements and calculations

MAP, systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and HR measurements were taken from pulsatile arterial pressure recordings with AcqKnowledge 3.7.0 (Biopac Systems). While the animals performed the exercise protocol, MAP, SAP, DAP and HR were registered every minute until fatigue.

Time to fatigue (min) and workload (kgm) were considered indexes of exercise performance. Workload (kgm) was calculated as follows: (body weight (kg)) × (total time to fatigue (min)) × (treadmill speed (m min^{-1})) × (sin θ (treadmill inclination) (Leite et al., 2006). Rate-pressure product (mmHg bpm), an indicator of myocardial oxygen demand, was calculated by multiplying SBP by HR (Pires et al., 2013).

2.6. Statistical analysis

The data are reported as mean ± S.D. A two-way analysis of variance (ANOVA) was used for determining on the one hand differences between time and treatment, and on the other hand the interactions between them. This was done in order to evaluate the differences in cardiovascular adjustments. Significant interactions observed by ANOVA were further evaluated by Newman-Keuls post hoc analysis to locate significant differences between means. Time to fatigue and workload were compared using paired Student's *t*-test. The correlation was assessed using Pearson's correlation coefficient. Significance level was set at $P < .05$. The above mentioned correlations were classified according to Evans's criteria as follows: 0.00–0.19, very weak; 0.20–0.39, weak; 0.40–0.59, moderate; 0.60–0.79, strong; and ≥0.80, very strong (Evans, 1996).

3. Results

3.1. Exercise performance

As expected, central AT_1 receptor blockade reduced running time to fatigue by 22% (14.5 ± 2.0 min losartan vs. 18.7 ± 1.5 min saline; $P \leq .00$) (Fig. 1a). Workload, another index of exercise performance, was also decreased after intracerebroventricular injections of losartan (3.1 ± 0.2 kgm losartan vs. 4,3 ± 0.5 kgm saline; $P \leq .00$).

3.2. Cardiovascular adjustments

As shown in Fig. 1a, exercise induced an increase in MAP already observed in control rats after1 min of running (124.4 ± 7.5 mmHg vs. 119.0 ± 6.7 mmHg; $P \leq .00$). MAP then remained elevated until fatigue. In rats treated with losartan, MAP also increased as soon as the exercise started (131.8 ± 5.9 mmHg vs. 122.2 ± 5.2 mmHg; $P \leq .00$) until the moment of fatigue. These rats had higher MAP than controls from 6 min of exercise, being the highest difference between groups observed at fatigue (140.5 ± 3.8 mmHg losartan vs. 126.0 ± 7.2 mmHg saline; $P \leq .02$). Such intense MAP response following after AT_1 receptor blockade was significantly greater than in controls at 40% of time to fatigue and remained elevated until the end of exercise (Fig. 1b). Moreover, even though the time elapsed from the beginning of exercise until MAP peak was similar between groups (8.0 ± 3.8 min losartan vs. 6.8 ± 2.6 min saline; $P \leq .30$), MAP peak was increased in losartan treated-rats (142.1 ± 3.8 mmHg losartan vs. 133.7 ± 6.0 mmHg saline; $P \leq .02$) (Fig. 2a). A very strong negative correlation was also shown between the reduced exercise time seen in losartan-rats and the MAP at the fatigue point ($r = 0.82$, $P \leq .01$) (Fig. 2b).

As shown in Fig. 3, exercise induced an increase in DAP after 2 (112.4 ± 12.6 mmHg vs. 105.3 ± 6.4 mmHg; $P \leq .05$) and 1 min (117.5 ± 4.6 mmHg vs. 109.0 ± 7.9 mmHg; $P \leq .02$) of exercise in control and losartan rats, respectively (Fig. 3b). However, while DAP remained elevated until fatigue after losartan treatment, it recovered to resting values after 9 min of exercise until fatigue in control animals. Losartan treated animals had higher DAP than controls from 4 min of exercise until fatigue (127.2 ± 7.2 mmHg losartan vs. 108.4 ± 3.4 mmHg saline; $P \leq .00$).

Similarly, SAP increased after 2 (145.8 ± 10.8 mmHg vs. 132.9 ± 11.0 mmHg; $P \leq .00$) and 1 min (144.4 ± 6.0 mmHg vs. 134.5 ± 5.4 mmHg; $P \leq .01$) of exercise until fatigue in control and losartan rats, respectively (Fig. 3a). Differences between groups were observed from 4 min of exercise until fatigue (160.2 ± 9.0 mmHg losartan vs. 145.3 ± 10.9 mmHg saline; $P \leq .04$). A strong negative correlation was also found between the reduced workload performed by losartan-rats and the DAP at the fatigue point ($r = 0.74$, $P \leq .01$) (Fig. 4a).

Running on the treadmill induced an increase in HR within 1 min of exercise in both control (452.6 ± 70.2 bpm vs. 397.4 ± 49.6 bpm; $P \leq .00$) and losartan treated-rats (457.1 ± 24.7 bpm vs. 396.6 ± 27.7 bpm; $P \leq .01$) (Fig. 3c). HR remained elevated throughout the exercise protocol, and differences between treatments were observed from 8 min of exercise (536.9 ± 28.3 bpm losartan vs. 497.6 ± 38.8 bpm saline, $P \leq .05$) until fatigue (542.8 ± 26.8 bpm losartan vs. 500.1 ± 42.9 bpm saline, $P \leq .05$).

The calculation of the rate-pressure product revealed that values already enhanced after 1 min of exercise for both losartan (63.0 ± 15.2 mmHg bpm/1000 vs. 53.1 ± 9.8 mmHg bpm/1000; $P \leq .01$) and saline (65.9 ± 2.3 mmHg bpm/1000 vs. 53.3 ± 4.0 mmHg bpm/1000; $P \leq .00$) treated rats. Losartan treated rats had higher rate-pressure product than control animals from 6 min of exercise until fatigue (86.9 ± 6.1 mmHg bpm/1000 losartan vs. 72.8 ± 9.4 mmHg bpm/1000 saline, $P \leq .03$). A strong negative correlation was also found between the reduced workload performed by losartan-rats and the rate-pressure product at the point of fatigue ($r = 0.78$, $P \leq .01$) (Fig. 4b).

4. Discussion

The present data shows that central AT_1 receptors blockade with intracerebroventricular losartan produces greater exercise-induced rise in MAP. Such intense increase was verified already at 40% of time to fatigue, and remained elevated until the end of exercise. Moreover, HR was also increased after losartan treatment throughout running

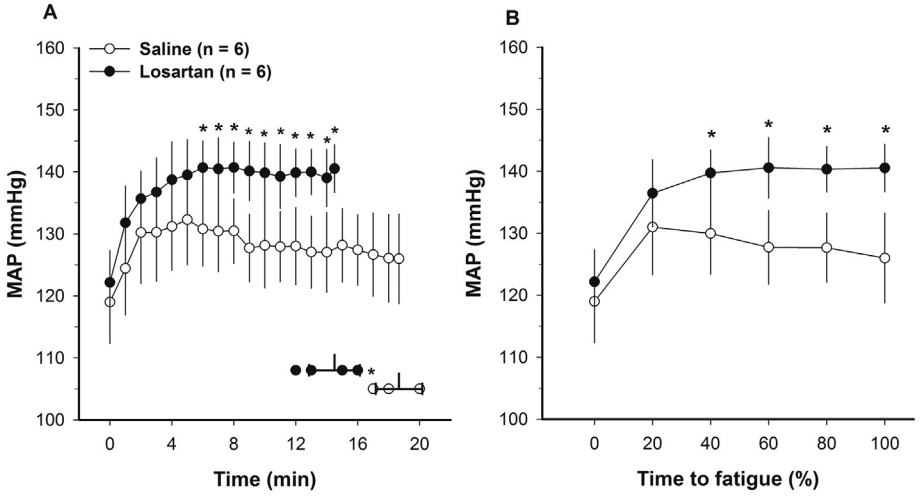

Fig. 1. Effect of intracerebroventricular injection of losartan (n = 6) or saline (n = 6) on mean arterial pressure (MAP) during running until fatigue (A) and MAP as a function of time to fatigue percentage (B). Time to fatigue is indicated by the dot plot at the bottom of graph 1A (samples of the 6 data points, the central line represents the mean value). Data are expressed as mean ± S.D. *$P < .05$ compared with saline-treated group.

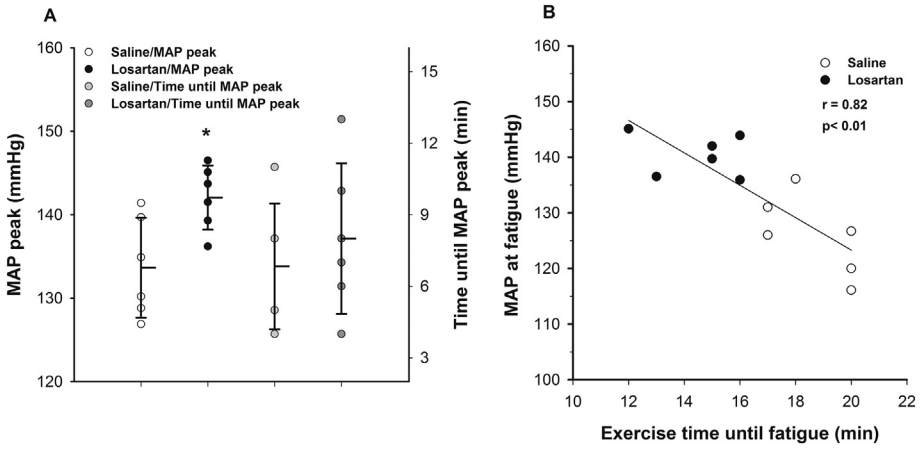

Fig. 2. Effect of intracerebroventricular injection of losartan (n = 6) or saline (n = 6) on mean arterial pressure (MAP) peak and time until MAP peak (A, samples of the 6 data points, the central line represents the mean value) and correlation between MAP at fatigue point and time to fatigue during running until fatigue (B). Data are expressed as mean ± S.D. *P < .05 compared with saline-treated group.

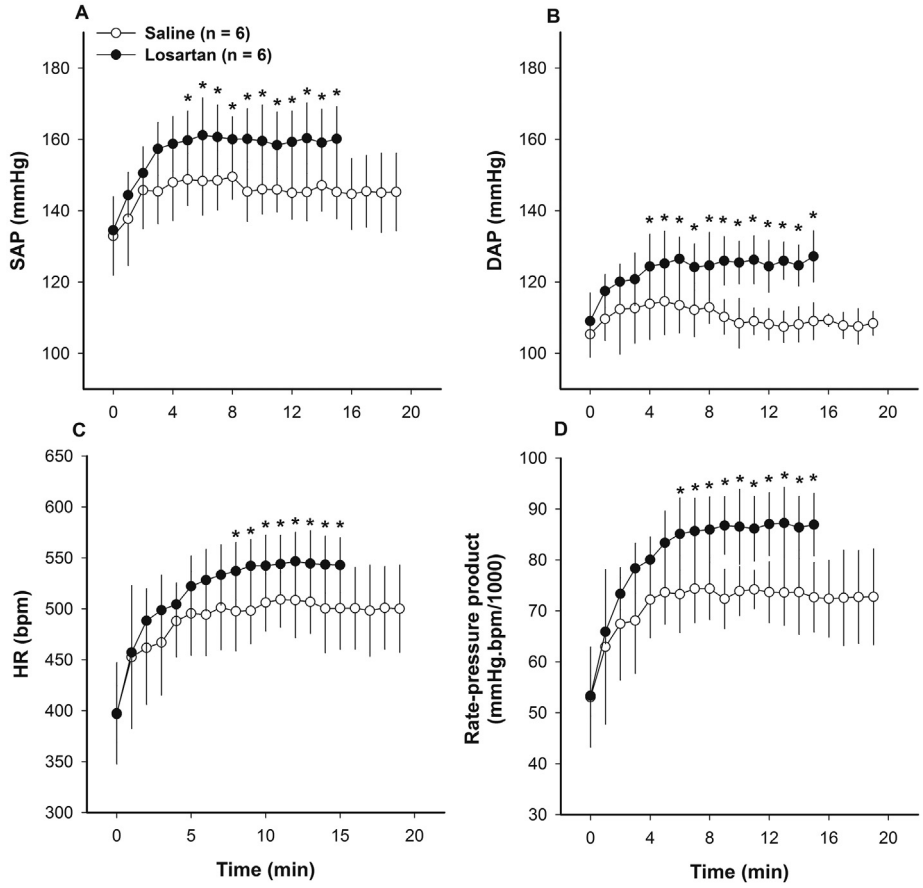

Fig. 3. Effect of intracerebroventricular injection of losartan (n = 6) or saline (n = 6) on diastolic arterial pressure (DAP) (A), systolic arterial pressure (SAP) (B), heart rate (HR) (C) and rate-pressure product (D) during running until fatigue. Data are expressed as mean ± S.D. *P < .05 compared with saline-treated group.

exercise. These results point to the direction of an augmented sympathetic outflow during exercise induced by central AT_1 receptors blockade, also supported by previous evidences that central angiotensinergic blockade determines an elevation of the body temperature threshold for tail vasodilation (Leite et al., 2006), as well as higher levels of plasma free fatty acids and glycolytic flux at low level of exercise intensity (Leite et al., 2009). Furthermore, the current data indicate that central angiotensinergic blockade-mediated decrease in exercise performance is simultaneous to the enhanced sympathetic-controlled blood pressure response to exercise. In fact, the higher exercise-induced increase in DAP and rate-pressure product seen after central AT_1 receptor blockade indicate a considerable challenge to cardiovascular homeostasis, which strongly indirectly correlates with the workload performed. Taken together, the experiments reported here demonstrate that central angiotensin II AT_1 receptors are involved in neuromodulation of exercise-induced cardiovascular adjustments in rats.

There distribution of blood flow among the tissues is the major cardiovascular response for the maintenance of physical activity. Exercise-induced increase in metabolic rate requires a higher cardiac output to match the metabolic demands of working muscles (Gonzalez-Alonso et al., 2008). There is also a redistribution of cardiac output to the skin to dissipate the heat produced (Fadel and Raven, 2012; Williamson et al., 2006). In order to promote such transfer of the blood

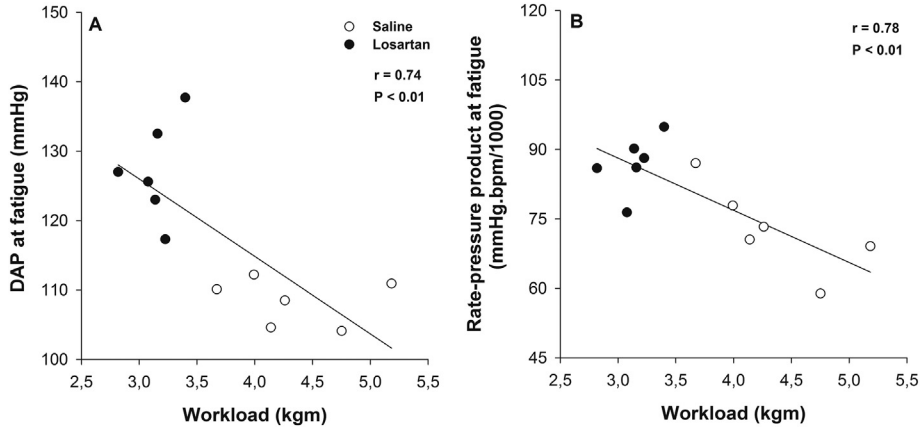

Fig. 4. Correlations between workload performed and diastolic arterial pressure (DAP) at fatigue (A) and rate-pressure product at fatigue (B).

volume, HR and MAP raise simultaneously, in parallel with a non-uniform, independent and selective redistribution of blood flow according to specific vascular beds (Gonzalez-Alonso et al., 2008; Leite et al., 2012; Morrison, 2001). These cardiovascular regulations mediated by exercise also rely primarily on changes in the neural control of the baroreflex pathway (Fadel and Raven, 2012; Dampney, 2017; Potts, 2006). Thus, the central command arising from the cortical areas and the feedback signals arising from different sensors in the periphery are integrated at the level of the nucleus tractus solitaries (NTS) to directly reset the baroreflex through a connection with glutamatergic neurons that in turn synapse with GABAergic neurons within the caudal ventrolateral medulla (CVLM). Such CVLM GABAergic neurons inhibit sympathetic premotor neurons within the rostral ventrolateral medulla (RVLM) that project to sympathetic preganglionic neurons within the intermediolateral cell column (IML) in the spinal cord, modulating its activity with glutamate (Dampney, 2017; Potts, 2006).

Although some evidences propose that the physiological role of angiotensin II in the cardiovascular adjustments to exercise, particularly the regulation of blood pressure and regional blood flow, depend on peripheral effects of increased circulating levels of angiotensin II as a consequence of exercise (Stebbins and Symons, 1995; Warren et al., 2001), the pronounced effects of this peptide on the regulation of sympathetic outflow from the central nervous system must be considered (Leite et al., 2009). In fact, it is well established that the brain produces angiotensin II and has AT_1 receptors diffusely located in many nucleus, including higher centers that modulate baroreflex, as well as the four key nuclei involved in the baroreflex pathway itself (Jackson et al., 2018; Khanmoradi and Nasimi, 2017). However, the fact that angiotensin II may access the brain though the circumventricular organs that lack blood brain barrier supports the premise that plasma angiotensin II may also influence brain-regulated cardiovascular functions (Jackson et al., 2018; Johnson and Gross, 1993). Even though it is still uncertain whether brain angiotensin II levels increase because of exercise, acting centrally, the peptide may lead to a reset of the arterial baroreflex and changes in sympathetic outflow (Warren et al., 2001; Mousa et al., 2008; Negrao and Middlekauff, 2008).

In the present study, intracerebroventricular blockade of AT_1 receptors with losartan resulted in higher increase in HR and in MAP, DAP and SAP during exercise. Moreover, although the temporal response was similar between control and losartan treated-rats, the magnitude of MAP peak was significantly increased after central AT_1 receptor blockade. This intense blood pressure response seen in rats injected with losartan suggests that central AT_1 receptors may exert inhibitory effects in a central pathway that stimulates sympathetic outflow during the initial minutes of exercise. Our data indicating that central angiotensin II AT_1 receptors blockade during exercise induces sympathetic activation precociously at a lower level of exercise intensity are in accordance with such findings (Leite et al., 2009). This is also reinforced by the present demonstration that losartan-rats had increased blood pressure response early at 40% of time to fatigue.

These results are consistent with the less explored role played by central AT_1 receptors on sympathoinhibition via the brain ventricular routes (De Luca Junior et al., 1994; De Luca Jr. et al., 1996). Evidences have shown that the injection of AT_1 receptors antagonist into either the anterior ventricles or into the fourth ventricle of rats increases arterial pressure (De Luca Junior et al., 1994; De Luca Jr. et al., 1996). Thus, besides its established role as a hypertensive agent, there is evidence that central angiotensin II also does the opposite (De Luca Jr. et al., 2000; Sugawara et al., 2002). The physiological role of angiotensin II-induced hypotension still require clarification, but one possible mechanism is the activation of central circuits that counteract increases in arterial pressure (De Luca Jr. et al., 2000; Sugawara et al., 2002). Therefore, it seems reasonable to suggest that losartan is hypothetically perfused to brainstem and hypothalamic regions after being injected into the cerebral ventricle, modulating central cardiovascular function by interfering on sympathetic tonus. The different ways in which baroreflex resetting may occur are vast. Still, it can probably occur via modulation of synaptic transmission to and/or within one or more of the key nuclei involved in the baroreflex pathway (Dampney, 2017; Khanmoradi and Nasimi, 2017). In this sense, we propose that the augmentating effect of losartan on the pressor response might be in part due to a neuromodulatory action on cell bodies of neurons through AT1 receptors, resulting in a decrease in firing rate and consequently in a pressor response (Dampney, 2017; Khanmoradi and Nasimi, 2017). The second neuromodulatory action of losartan might be at synaptic connections between the axon and the cell body. AT1 receptor blockade might act at receptors on the presynaptic terminals to adjust the release of a neurotransmitter, thereby facilitating an inhibitory signal that ultimately could lead to increased drive to sympathetic neurons (Dampney, 2017; Khanmoradi and Nasimi, 2017).

The current data also support experiments showing that central injection of losartan limits exercise performance (Leite et al., 2013). Our previous studies confirmed that one predictor of central losartan-induced fatigue is the development of intense hyperthermia characterized by increased metabolic rate and decreased heat loss (Leite et al., 2006, 2007). Specifically, heat loss is jeopardized by the delayed activation of tail heat loss mechanism, which we have previously shown to occur at higher body temperatures in losartan-treated rats during exercise probably due to increased sympathetic activation (Leite et al., 2006, 2009). In the present study, central angiotensinergic blockade produced an intense increase in MAP followed by tachycardia, also pointing to the direction of an augmented sympathetic outflow during exercise. Therefore, the thermal imbalance induced by central AT1 receptors blockade during exercise (Leite et al., 2006, 2007) seems to

occur in parallel with an increased cardiac strain. Actually, tail vasodilation is also modulated by non-thermic stimulus, such as arterial baroreceptors activation (Johnson and Gilbey, 1998; Zhang et al., 2003). Such interaction ultimately may affect heat dissipation through the tail and reflect on exercise performance (Leite et al., 2006, 2007). The delayed cutaneous vasodilation increases the rates of body heating and heat storage, contributing to the reduced performance of these animals in order to protect the brain from thermal damage (Leite et al., 2006; Coimbra et al., 2012). Considering these effects of central losartan on cardiovascular adjustments and, consequently, on heat balance, keeping up the same intensity effort during physical exercise could lead to a harmful situation in which the heat dissipated would be insufficient to compensate for the heat produced.

In this sense, the present data supports that the decreased time to fatigue seen after central AT_1 receptor blockade courses in parallel with the greater MAP response to exercise. In fact, the intense increase of DAP and rate-pressure product shown by losartan-treated rats strongly inversely correlated with the workload performed. Therefore, it appears that central losartan treatment provides a considerable challenge to cardiovascular homeostasis, probably also as a result of a rise in myocardial oxygen consumption, which contributes to exercise intolerance (Guazzi et al., 2001; Missault et al., 1993). In this case, it is possible that the inferior exercise capacity induced by central angiotensin II inhibition is the result of impairment of both hemodynamic, such as systolic function, and blood flow redistribution to the myocardium, skeletal muscles and skin (Warren et al., 2001). The combination of these effects probably decreased active muscles blood flow, reducing oxygen availability, as well as cutaneous blood flow, deteriorating heat dissipation. Given that central losartan also aggravates the exercise-induced hyperthermia (Leite et al., 2006, 2007), the thermoregulatory demands to increase skin blood flow and the metabolic demands to increase muscle blood flow could both be high. Thus, the heart could be unable to fill with or pump out enough blood to meet such intense demands, leading to the interruption of exercise since the limits of cardiac pumping capacity could be exceeded (Gonzalez-Alonso et al., 2008).

5. Conclusions

In conclusion, intracerebroventricular angiotensin II blockade increases cardiac strain during exercise and decreases time to fatigue, however, the mechanism is still unknown. The present data indicate that central angiotensinergic transmission is involved in neuronal circuitry that controls blood pressure adjustments in rats, probably by modulating sympathetic outflow during exercise. Given that losartan is widely prescribed to patients with high blood pressure, kidney disease, and heart failure (Terra, 2003), this study brings further evidence of cardiovascular effects of this drug during exercise.

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Declaration of Competing Interest

None.

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