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Chronic sympathectomy of the caudal artery delays cutaneous heat loss during passive heating

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HIGHLIGHTS

- Caudal artery denervation slows down cutaneous heat loss during heat exposure.
- Caudal artery denervation decreases the temperature variability of tail skin.
- The variability of the core temperature is not altered by caudal artery denervation.
- No signs of reinnervation were observed 30 days after caudal artery denervation.
- Sympathetic innervation provides fine-tuned control over cutaneous heat loss.

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ABSTRACT

The present study aimed to investigate the chronic effects of caudal artery sympathectomy on thermoregulatory adjustments induced by passive heating. Male Wistar rats were subjected to two surgical procedures: caudal artery denervation (CAD) or sham surgery (Sham-CAD) and intraperitoneal implantation of a temperature sensor. On the day of the experiments, the animals were exposed to an ambient temperature of 36 °C for 60 min or allowed to rest under thermoneutral conditions (26 °C). During the experiments, the tail skin temperature (T_{skin}) and the core body temperature (T_{core}) were measured. Under thermoneutral conditions, although sympathetic denervation did not change the average values of T_{core} and T_{skin}, CAD rats exhibited decreased T_{skin} variability compared with Sham-CAD rats (0.020 ± 0.005 °C vs. 0.031 ± 0.005 °C; $P = 0.024$). During heat exposure, no differences were observed in the T_{core} between the groups. In contrast, although peak T_{skin} values were not affected by chronic sympathectomy of the caudal artery, CAD animals showed a delayed increase in T_{skin}; the time until the stabilization of T_{skin} was three-fold longer in CAD rats than in Sham-CAD rats (15.3 ± 2.5 min vs. 4.9 ± 0.6 min; $P = 0.001$). In conclusion, chronic sympathectomy of the caudal artery delays cutaneous heat loss during passive heating and decreases T_{skin} variability under thermoneutral conditions. Taken together, our results indicate that the sympathetic innervation of cutaneous vessels is essential for the precise regulation of tail heat loss.

1. Introduction

Some pathological conditions (e.g., spinal cord lesions or diabetic neuropathy) and sympathectomy of the upper limbs (used as a treatment for palmar hyperhidrosis) change the perivascular neural environment and, consequently, the regulation of blood flow in the skin [2,9,12]. The sympathetic denervation of cutaneous vessels promotes a transitory increase in skin blood flow that is followed by a progressive and persistent decrease [23]; this late reduction of cutaneous blood flow has been related to functional and structural adaptations that favor greater constriction of the denervated vasculature [1,17,19,21,23]. Because the regeneration of the sympathetic axons innervating the distal vessels is slow and incomplete [3], lesions in the cutaneous vascular nerves can make the skin cold, cyanotic, and susceptible to injury (i.e., ulceration) [12,20].

Several methodological approaches, such as surgical procedures [7,23], pharmacological treatments [17] and studies in

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patients and animals with nerve injuries [4,12], have been performed to investigate both the acute and chronic adaptations induced by vascular denervation. Although these studies have enhanced the knowledge about the effects of sympathetic innervation, the results of such studies cannot be attributed solely to the lack of vascular innervation. In pathological models, the results are also associated with a loss of cutaneous sensorial innervation and/or vascular dysfunctions inherent to the diseases. Furthermore, the wide-spread side effects evoked by the systemic administration (i.e., intravenous or intraperitoneal administration) of pharmacological agents or the concomitant denervation of the vascular beds of the feet induced by lumbar sympathectomy surgery can also affect the experimental outcomes [6,7]. Therefore, to avoid the limitations of the experimental approaches employed so far, we developed a surgical procedure that allowed us to exclusively investigate the effects of sympathectomy on a specific blood vessel. For this purpose, a phenol solution was topically applied around the proximal portion of the caudal artery. The application of phenol induces fast and long-lasting nerve degeneration [22].

The cutaneous vessels in the rat's tail play an important role in the control of heat exchange between the body surface and the environment. Cutaneous blood flow is primarily under the control of the sympathetic vasoconstrictor nerves [7], and in thermoneutral environments, core body temperature (T_{core}) regulation is largely dependent on nonevaporative physical processes that include fluctuations in skin blood flow [11]. Dysfunctions in thermoregulatory adjustments have been described in animals and human patients with spinal cord injuries, in individuals subjected to sympathectomy of the upper limbs and in patients with diabetic neuropathy [9,12]; however, because other mechanisms can interfere with these responses (lack of cutaneous sensorial innervation, lack of sweat gland innervation, and changes in temperature sensitivity), the exclusive contribution of sympathetic vascular innervation to body temperature control has yet to be conclusively determined. Taking these facts in account, the present study aimed to investigate whether the cutaneous heat loss of freely moving animals in a neutral environment is changed by chronic sympathectomy of the caudal artery.

Kalincik et al. [4] reported that during cold exposure, the magnitude of the tail skin temperature (T_{skin}) reduction was not changed in rats with spinal cord lesions, suggesting that a higher sensitivity to humoral and local vasoconstrictor agents could have compensated for the absence of neurovascular control in this environment. Alternatively, it is possible that vascular adaptations favoring vasoconstriction could impair cutaneous heat loss in warm environments, consequently increasing the risk of heat-related lesions. However, no study has determined whether the thermoregulatory adjustments induced by heat exposure are modified by chronic sympathectomy of the caudal artery. This was the second objective of the present study.

2. Materials and methods

All experimental procedures were approved by the Ethics Committee of the Universidade Federal de Minas Gerais for the Care and Use of Laboratory Animals (protocol 109/09) and were carried out in accordance with the policy described in the Committee's Guiding Principles Manual.

The experiments were performed on 26 male Wistar rats weighting 210–240 g at the time of sympathectomy. Animals were housed in individual cages and kept in a room with controlled light (05:00–19:00 h) and temperature (24.0 ± 1.0 °C) conditions. Standard rat chow and tap water were provided *ad libitum*. Initially, the rats were subjected to caudal artery denervation (CAD) or Sham-CAD as a control procedure. Three weeks later, a temperature sensor (TR3000 XM-FM; Mini-Mitter, Sun River, OR, USA) was implanted into the peritoneal cavity, and after recovery from this surgery, the rats were subjected to two experimental trials: resting under thermoneutral conditions (26 °C) or heat exposure (36 °C).

The surgical procedures were performed under ketamine-xylazine anesthesia (116 and 6 mg/kg body mass, respectively, i.p.). Immediately after the surgeries, the rats received an intramuscular prophylactic dose of antibiotics (pentabiotic, 48,000 IU/kg body mass) and a subcutaneous injection of analgesic medication (flunixin meglumine, 1.1 mg/kg body mass).

Caudal artery denervation. The caudal artery was exposed by two 8 cm ventral incisions starting from the base of the tail: the first incision was made in the skin, followed by another in the subcutaneous tissue. After being visualized, the caudal artery was gently dissected from its surrounding tissue; care was taken to avoid sectioning the arteriovenous anastomosis. Then, the caudal artery was painted with a topical 10% phenol solution (diluted in glycerol), and the tail skin was sutured with absorbable thread (4.0). During the Sham-CAD surgery, the 8 cm ventral incision in the tail skin surface was made, and the skin surface was sutured without compromising any vascular innervation.

Implantation of temperature sensors. A 2 cm ventral incision was made in the *linea alba* of the abdominal muscle, allowing for the insertion of a temperature sensor in the peritoneal cavity [8]. Following the insertion, the abdominal muscle and skin were sutured in layers. All animals were allowed to recover for 4 days before being subjected to the experiments.

On the day of the experiments (26–28 days after CAD or Sham-CAD surgery), each rat was weighed, a thermocouple was fixed to its tail surface, and the rat was placed inside an acrylic chamber (49.5 cm long × 14 cm wide × 13.5 cm high). An electrical fan positioned at one end of the chamber generated an air flow rate of 2.0–2.5 m/min. To heat the environment inside the chamber, an electrical heater (Britânia model AB 1100, Curitiba, PR, Brazil) was positioned at the same level 20–30 cm distant from the fan and turned on at 1200 W.

During resting at 26 °C, T_{core} and T_{skin} were recorded for 60 min after their levels had stabilized; during heat exposure, the thermoregulatory parameters were recorded immediately after the animals were placed inside the environmental chamber. The intraperitoneal temperature was measured by telemetry and considered to be the T_{core} index. T_{skin} was measured on the lateral surface ~1 cm from the base of the tail [24] using a thermocouple. T_{core} values were recorded every 10 s, whereas T_{skin} and T_a inside the chamber were recorded every min throughout the experiments. The heat loss index (HLI) was used to determine if the ambient temperatures studied corresponded to neutral or supra-neutral conditions in our experimental setup [11] and calculated as $[T_{skin} - T_a]/[T_{core} - T_a]$. To analyze the variations in both T_{core} and T_{skin}, we calculated their coefficients of variation as [average standard deviation/pre-experimental values] (variability index 1) or their average standard deviation throughout experiments (variability index 2).

Glyoxylic acid fluorescence histochemical method. At the end of the experiments (30 days after the CAD or Sham-CAD surgery), the rats were anesthetized with ketamine-xylazine (116 and 6 mg/kg body mass, respectively, i.p.), and 2 cm-long samples of the caudal artery were removed by ventral incisions at the base, middle and tip of the tail. The samples were analyzed using two different protocols: half of them were stored in −80 °C freezer, and the other half were immediately analyzed. The first protocol was conducted to determine the location of sympathetic innervations in the caudal artery, and the second protocol was conducted to determine the density of the sympathetic innervations in the caudal