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# Sympathetically induced renal vasoconstriction during stimulation of mesencephalic locomotor region in rats

Satoshi Koba [a], Takayoshi Yoshida [a,b], Naoyuki Hayashi [c,*]

[a] *Graduate School of Engineering Science, Osaka University, 1-3 Machikaneyama-cho, Toyonaka, Osaka, 560-8531, Japan*
[b] *School of Health and Sport Sciences, Osaka University, 1-17 Machikaneyama-cho, Toyonaka, Osaka, 560-0043, Japan*
[c] *Institute of Health Science, Kyushu University, 6-1 Kasuga-Kouen, Kasuga, Fukuoka, 816-8580, Japan*

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**Abstract**

Central command, which is a neural drive originating in the brain during exercise, regulates the sympathetic nervous system and evokes cardiovascular responses to exercise. To examine the role of the central command on sympathetic regulation of renal circulation, we compared responses in renal cortical blood flow and vascular conductance to electrical stimulation of mesencephalic locomotor region (MLR) for 30 s in decerebrate and paralyzed rats between renal nerves that were intact ($n=8$) and denervated ($n=8$). In rats with renal nerves intact, stimulation of the MLR at 40 μA current intensity significantly ($p<0.05$) decreased renal cortical blood flow ($-17\pm5\%$, means ± S.E.M.) and vascular conductance ($-43\pm4\%$) and the decrease in renal vascular conductance was dependent on current intensity (between 20 and 60 μA). In renal denervated rats, in contrast, there were no significant changes in either renal cortical blood flow or vascular conductance during stimulation at all current intensities. In a subset of rats ($n=8$), the response in renal sympathetic nerve activity to 30 s stimulation of the MLR was investigated. Stimulation of the MLR significantly increased renal sympathetic nerve activity ($+57\pm14\%$ at 40 μA) and the response was dependent on current intensity (between 20 and 60 μA). These data provide evidence that central command induces renal vasoconstriction by increasing sympathetic activity, depending on central command intensity.


*Keywords:* Exercise; Central command; Renal cortical blood flow; Renal sympathetic nerve activity

## 1. Introduction

Two principle neural mechanisms, i.e., exercise pressor reflex (Kaufman and Forster, 1996) and central command (Waldrop et al., 1996), have been proposed to increase sympathetic nerve activity (SNA) and adjust cardiovascular system during exercise. The exercise pressor reflex is a feedback neural drive which originates from metabolic and mechanical activation of afferent nerve endings located in contracting skeletal muscles (Kaufman and Forster, 1996). Central command is a feedforward neural drive which involves a parallel activation of the brain stem that controls locomotor and cardiorespiratory activities (Waldrop et al., 1996). The hypothalamic locomotor region (HLR) (Eldridge et al., 1985), mesencephalic locomotor region (MLR) (Bedford et al., 1992), and several cortical tissues (Critchley et al., 2000; Thornton et al., 2002; Williamson et al., 2002, 2003) are identified as possible origins of central command.

In humans at rest, the kidneys receive blood flow at about 20% of cardiac output (Rowell, 1993). During exercise, blood flow to exercising skeletal muscles increases, while that to the visceral organs including the kidneys decreases (Diepstra et al., 1982). The changes in blood flow are believed to be an attempt to match the increased metabolic demand in the exercising muscles. Thus, renal vasoconstriction contributes to the maintenance of blood pressure and the distribution of blood flow toward the muscles during exercise. Renal circulation is largely regulated by renal sympathetic nerve activity (RSNA) during exercise (Hohimer and Smith, 1979; Mueller et al., 1998). RSNA increases during exercise and is related to

* Corresponding author. Tel./fax: +81 92 583 7848.
*E-mail address:* naohayashi@ihs.kyushu-u.ac.jp (N. Hayashi).

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exercise intensity (Miki et al., 2002; O'Hagan et al., 1993; Schad and Seller, 1975). The exercise pressor reflex and/or central command can be considered as neural triggers to increase RSNA and to induce renal vasoconstriction (Middlekauff et al., 1997). The role of the exercise pressor reflex on sympathetic regulation of renal circulation has been demonstrated in cats (Matsukawa et al., 1992) and humans (Middlekauff et al., 1997; Momen et al., 2003). The exercise pressor reflex induces renal vasoconstriction through an increase in RSNA (Matsukawa et al., 1992; Middlekauff et al., 1997; Momen et al., 2003). On the other hand, the role of central command is not fully understood. Previous studies have shown that central command increases RSNA (Dean and Coote, 1986; Hajduczok et al., 1991; Hayes and Kaufman, 2002) and decreases renal blood flow (Waldrop et al., 1986). However it has not been demonstrated whether central command induces sympathetic vasoconstriction in the kidney.

The present study was designed to examine the role of central command on the sympathetic regulation of renal circulation and the effect of central command intensity on the renal sympathetic and circulatory responses. We observed the responses in renal cortical blood flow (RCBF) and renal cortical vascular conductance (RCVC) to graded levels of electrical stimulation of the MLR in decerebrate and paralyzed rats with the renal nerves intact and denervated. Moreover, in a subset of rats, we observed RSNA responses to graded levels of stimulation of the MLR.

## 2. Materials and methods

### 2.1. General

All experimental procedures of the present study were approved by the Research Ethic Committee of the School of Health and Sport Sciences, Osaka University and were conducted in accordance with the Guiding Principles in the Care and Use of Animals in the Fields of Physiological Sciences published by the Physiological Society of Japan. Twenty-four male Sprague–Dawley rats (7–9 weeks, weight: 250–350 g) were used in the present study. The rat was anesthetized with a mixture of halothane (<4%) and oxygen. The trachea was cannulated and then the lungs were artificially ventilated with a respirator (SN-480-7, Shinano, Japan) at 60–70 times per minute in frequency and 2 ml in tidal volume. The left jugular vein and common carotid artery were also cannulated to administer drags and to measure arterial pressure (AP), respectively. The carotid artery catheter was attached to a pressure transducer (P23XL-1, Ohmeda, USA). Arterial pH was continually measured with a pH meter (B-212, Horiba, Japan). It was maintained within normal limits by infusing sodium bicarbonate solution intravenously or by changing the ventilation frequency. Two syringe needles were set in the back to measure the electrocardiogram (ECG). The variable was amplified with a differential amplifier (AB-621G, Nihon Kohden, Japan). Heart rate (HR) was calculated beat to beat by detecting the time between successive R waves in the ECG. Body temperature was adequately maintained with a heating lamp.

### 2.2. RCBF recording

In 16 rats, RCBF was recorded. The left kidney was exposed retroperitoneally through the left trunk incision. The left RCBF was measured with a laser-Doppler flowmetry with a needle-type probe (ALF21, Advance, Japan), which measures blood flow within a 1 mm radius from the tip of the probe. The probe was placed and stabilized vertically on the dorsal surface of the kidney. In 8 rats of the 16, all visible left renal nerves were dissected (RD group).

### 2.3. RSNA recording

In another 8 rats, RSNA was recorded. A visible bundle of renal nerves was carefully dissected from other connective tissues. A piece of laboratory film was placed under the isolated nerve bundle and two tips of a bipolar electrode to measure RSNA were placed between the nerve bundle and the film. The third tip of the electrode was attached with the adipose tissue near the nerve bundle, which served as a grounding electrode. The exposed nerve bundle and the tips were embedded in a silicon gel. Once the silicon gel hardened, the silicon rubber was fixed to the surrounding tissue with a glue containing alpha-cyanoacrylate. The signal of RSNA was amplified with a differential amplifier (MEG2100, Nihon Kohden, Japan) with band-pass filters at 150 Hz low-cut frequency and 1 kHz high-cut frequency and made audible with an amplifier. RSNA was confirmed by observing the decreased and increased activities during the intravenous infusion of phenylephrine (5 μg) and nitroprusside (5 μg), respectively.

### 2.4. Decerebration

The rat was placed in a stereotaxic apparatus (ST-7, Narishige, Japan). Decerebration was performed with a modified method reported in a previous study (Hayashi, 2003). Dexamethasone (0.2 mg) was given intravenously to minimize brain edema. Immediately before the decerebration, the right carotid artery, not used for recording of AP, was occluded to reduce brain bleeding. The upper skull and dura matter were removed and then the cortical tissue was removed with an aspirator. After the site of superior and inferior colliculus was confirmed, the brain was sectioned vertically with a blade at 2.0 mm rostral from the junction of superior and inferior colliculus. All neural tissue rostral to the section and the cortical tissues covering the cerebellum were aspirated. Immediately after the decerebration, the halothane anesthesia was withdrawn. The cranial vault was filled with mineral oil. To replace the blood lost during decerebration (approximately <1 ml), saline was given