Autonomic Neuroscience: Basic and Clinical 189 (2015) 16–24

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

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

Stimulation of the mesencephalic ventral tegmental area blunts the sensitivity of cardiac baroreflex in decerebrate cats

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ARTICLE INFO

Article history:
Received 4 July 2014
Received in revised form 17 November 2014
Accepted 24 December 2014

Keywords:
Cardiac baroreflex sensitivity
Ventral tegmental area
Substantia nigra
Central command
Exercise

ABSTRACT

We have examined for the first time whether electrical stimulation of the mesencephalic ventral tegmental area (VTA) or the substantia nigra (SN) was capable of suppressing cardiac baroreflex sensitivity in decerebrate cats. After decerebration was performed by electrocoagulation at the precollicular–premammillary level and inhalation anesthesia was stopped, the animals were able to show spontaneous motor activity intermittently. Electrical stimulations of the mesencephalic areas (the VTA and SN) for 30 s were conducted with a monopolar tungsten microelectrode (current intensity of pulse trains, 50–100 μA; frequency, 40–50 Hz; pulse duration, 0.5–1.0 ms), without producing tibial motor discharge. Stimulation of the VTA evoked the significant increases in heart rate (HR, 12 ± 2 beats/min) and mean arterial blood pressure (MAP, 12 ± 3 mm Hg). When the baroreflex bradycardia and the slope of the cardiac baroreflex curve were examined using a pressor response with brief occlusion of the abdominal aorta, the VTA stimulation blunted both the baroreflex bradycardia and the maximal slope of the baroreflex MAP-HR curve by 63–74% in the same manner as spontaneously-evoked motor activity. In contrast, stimulation of the SN elicited no modulation of cardiac baroreflex. It is likely that stimulation of the mesencephalic VTA suppresses cardiac baroreflex sensitivity and has the similar features of the effects on the cardiac baroreflex function as those during spontaneously-evoked motor activity.

1. Introduction

A central mechanism originating from higher brain centers (termed central command) plays an important role in controlling the cardiovascular system during exercise (Goodwin et al., 1972; Mitchell, 1990, 2013). Gandevia et al. (1993) revealed using totally conscious but paralyzed human subjects that motor efforts are able to produce the similar cardiovascular response as actual motor performance. However, detailed information of central circuits and descending pathways about central command remains to be solved.

The sympathetic nerve and cardiovascular responses occur immediately before or at the onset of spontaneously-evoked body movement or locomotion in decerebrate cats (Eldridge et al., 1981; Matsukawa et al., 1998; Sadamoto and Matsukawa, 1997). Since the decerebration surgery disconnected the cerebral cortex and rostral diencephalon from the lower brainstem, the findings suggest that central command may generate in the caudal part of the diencephalon and/or regions within the brainstem. As one candidate for the brain sites generating central command, we proposed the mesencephalic ventral tegmental area (VTA) (Matsukawa, 2012). Several laboratories including us have studied the cardiovascular effects of electrical and chemical stimulation of the VTA. Electrical stimulation of the VTA evoked a pressor response, renal vasoconstriction, and skeletal muscle vasodilatation in anesthetized rabbits, cats, and rats (Matsukawa et al., 2011; Tan et al., 1983). Chemical stimulation of the VTA by a tachykinin agonist induced a pressor response and tachycardia in conscious rats (Cornish et al., 1997; Deschamps and Couture, 2005), whereas chemical stimulation of the VTA by L-glutamate produced a depressor response and bradycardia in anesthetized rats (Kirouac and Ciriello, 1997). Recently, we have reported using unanesthetized, decerebrate rats that chemical activation of neurons in the VTA is capable of eliciting synchronized stimulation of renal sympathetic and tibial motor nerves in concert with skeletal muscle vasodilatation (Nakamoto et al., 2011). Thus it is conceivable that the mesencephalic VTA plays a crucial role in generating central command.

On the other hand, it is known that a reduction in the cardiac baroreflex sensitivity occurs at the onset of ergometer exercise in humans (Bristow et al., 1969; Staessen et al., 1987). Such attenuating effect of exercise on the baroreflex bradycardia in response to aortic nerve stimulation was seen immediately before the onset of static exercise in conscious cats (Komine et al., 2003; Matsukawa et al., 2006). These findings suggest that central command plays an important role in blunting the sensitivity of the aortic baroreceptor-heart rate (HR) reflex and thereby contributing to an instantaneous increase in HR. If the mesencephalic VTA may play a crucial role in generating central command, it is expected that activation of neurons in the VTA should blunt the sensitivity of arterial blood pressure–HR curve. To test this hypothesis,

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http://dx.doi.org/10.1016/j.autneu.2014.12.005
1566-0702/

we attempted to examine whether electrical stimulation of the mesencephalic VTA or the substantia nigra (SN) attenuated the cardiac baroreflex sensitivity during the pressor intervention by brief aortic occlusion in unanesthetized, decerebrate cats. Furthermore, we attempted to compare the effects on the cardiac baroreflex function between the VTA stimulation and spontaneously-evoked motor activity.

2. Methods

The present study was conducted using 2 male and 5 female cats (body weight, 3.0 ± 0.1 kg) in accordance with the "Guiding Principles for the Care and Use of Animals in the Fields of Physiological Sciences" approved by the Physiological Society of Japan and the Guideline for Animal Experiment in Hiroshima University. The experimental protocols were approved by the Committee of Research Facilities for Laboratory Animal Science, Natural Science Center for Basic Research and Development, Hiroshima University.

2.1. Preparations

The animals were placed in a small box and anesthetized by inhaling a gas mixture of 4% halothane–N_2O (0.5 L/min)–O_2 (1.0 L/min). After induction of anesthesia, an endotracheal tube was inserted into the airway and the animal spontaneously breathed or the lungs were artificially ventilated with 0.5–1.0% halothane through the endotracheal tube, to implant catheters, perform decerebration surgery, and isolate the aortic nerve. An electrocardiogram (ECG), heart rate (HR), and thoracic respiratory movement were monitored throughout the experiments. To maintain a surgical level of anesthesia, the concentration of halothane was increased to 1.5–2.5% if HR and/or respiration spontaneously increased and/or if limb withdrawal occurred in response to a noxious pinch of the paw. Polyvinyl catheters were inserted into the left external jugular vein for administering drugs and into the left carotid artery for measuring arterial blood pressure (AP). The arterial catheter was connected to a pressure transducer (DPT-6100, Kawasumi Laboratories, Tokyo, Japan). HR was derived from the R wave of the ECG with a tachometer (model 1321, GE Marquette Medical Systems, Tokyo, Japan). Rectal temperature was maintained at 37–38 °C with a heating pad and a lamp. The left tibial nerve innervating the triceps surae muscle was dissected at the popliteal fossa in all cats. For measurement of tibial motor nerve activity, the tibial nerve bundle was placed on a pair of Teflon-coated silver-wire electrodes and then the peripheral portion of the nerve bundle was ligated. The original tibial motor activity was amplified by a differential preamplifier (S-0476, Nihon Kohden, Tokyo, Japan) with a band-pass filter of 50 and 3000 Hz. The amplified output was rectified and integrated with a resistance–capacitance integrator having a time constant of 20 ms.

The head of the cat was then mounted on a stereotaxic frame (SN-2N, Narishige, Tokyo, Japan). Decerebration was performed by electrocoagulation at the precollicular–premammillary level as previously described (Matsukawa et al., 1998; Sadamoto and Matsukawa, 1997). To do this, a stainless steel electrode with insulation removed 5 mm from the tip was inserted into the hypothalamus rostral to the mammillary bodies [coordinates from the midpoint of interaural line: anterior 13 mm, horizontal 6 mm, lateral 1–11 mm with an angle of 14° from perpendicular line; from stereotaxic atlases (Berman, 1968; Snider and Niemer, 1961)]. A negative DC current (1 mA) was passed through the electrode for 30 s. The electrode was withdrawn 4 mm and the current was passed again. This procedure was bilaterally repeated for a total of 42 tracks at 0.5 mm intervals.

2.2. Electrical stimulation of the VTA or the SN

Electrical stimulations of the ventral mesencephalic areas (the VTA and the SN) were conducted with a monopolar tungsten microelectrode (tip diameter 5 μm; shaft diameter 0.2 mm; UJ-3002, Unique Medical, Tokyo, Japan), which was stereotaxically inserted into the mesencephalic ventral areas according to the atlases of the cat brainstem (Berman, 1968; Snider and Niemer, 1961). An indifferent ground electrode was inserted in the occipital muscle. The current intensity of electrical pulse trains was 50–200 μA for 30 s at a frequency of 40–50 Hz and the duration of each pulse was 0.5–1.0 ms as previously reported (Matsukawa et al., 2011). At the end of the experiments, a small lesion was made by passing a negative DC current of 100 μA for 30–40 s to identify the stimulated site as demonstrated in Fig. 1. Then the animal was killed with an overdose of pentobarbital sodium. After

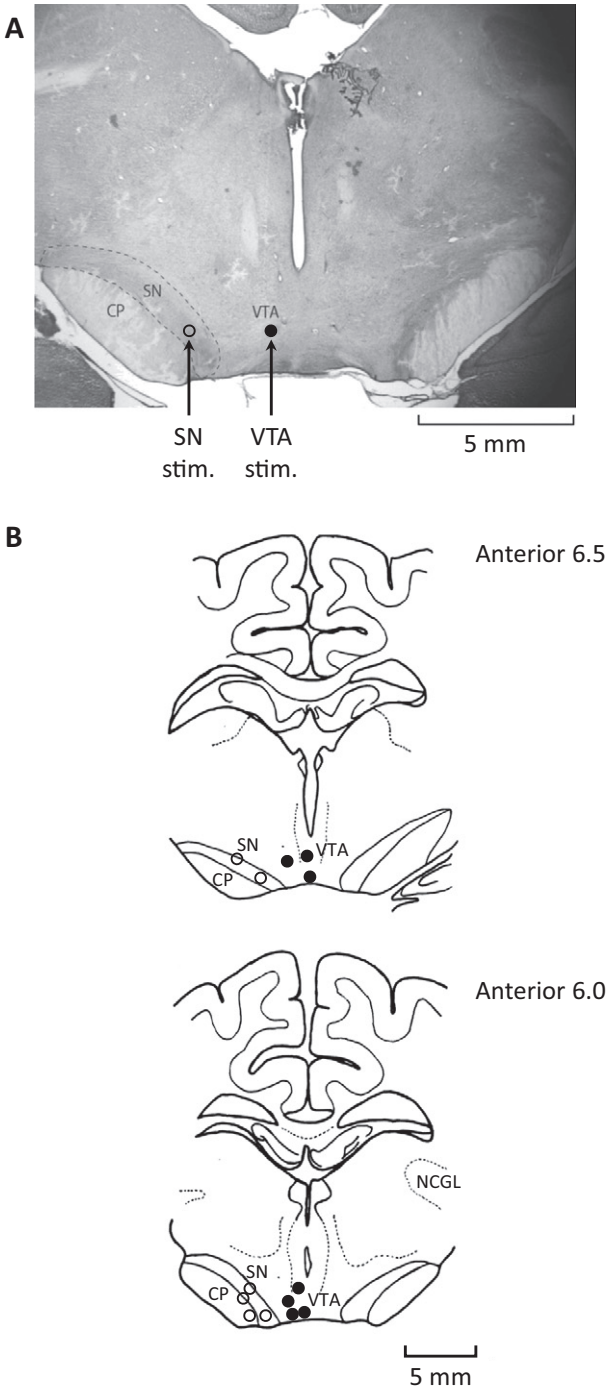

Fig. 1. A: an example of the stimulation sites (as indicated by circles) in the mesencephalic ventral tegmental area (VTA) and substantia nigra (SN). B: all locations of the electrodes for stimulating the VTA (●) and the SN (○). CP, cerebral peduncle. NCGL, nucleus corporis geniculate lateralis.