The Brain Histaminergic System in Regulating the Cardiovascular System: Implications for Brain Mechanisms Underlying Exercise–Induced Cardiovascular Responses

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A single bout of exercise induces a moderate increase in arterial pressure with marked tachycardia as a result of sympathoexcitation. However, the brain mechanisms underlying cardiovascular regulation during exercise still remain unknown. In this proceeding, we introduce our hypothesis that the brain histaminergic system plays an important role in regulating the cardiovascular system during exercise. The nucleus of the solitary tract (NTS) is one of the ideal brain sites for generating cardiovascular controls during exercise because it is known as a pivotal region which integrates the baroreceptor sensory information with other inputs such as muscle afferents and descending signals from the hypothalamic area. We found that activation of histamine receptor H1 expressed in the NTS neurons induced pressor and tachycardiac responses, and that the pressor response exhibited functional plasticity after long-term daily exercise. These findings suggest that H1 receptors in the NTS are involved in cardiovascular regulation during exercise. Since the NTS receives axons of histaminergic neurons located in the tuberomammillary nucleus (TMN) in the hypothalamus, the functional roles of TMN–NTS pathway have also been investigated. We electrically stimulated the TMN and found pressor and tachycardiac responses. Notably the pressor responses were partially inhibited by cetirizine, a H1 receptor antagonist, microinjected into the NTS whereas we failed to see the inhibitory effects on the heart rate response. Based on all these findings, we postulate that the TMN–NTS pathway has an important role in a central feed forward mechanism underlying pressor responses to exercise.

Key words: exercise, blood pressure, nucleus of the solitary tract, tuberomammillary nucleus, histamine

Typical pattern of cardiovascular responses during exercise and its regulatory mechanisms

The pattern of hemodynamic responses is complicated because it is affected by exercise type, intensity, and time. However, it is generally accepted that a single bout of exercise induces a mild increase in arterial pressure (AP) and marked tachycardia. These cardiovascular responses are mainly due to sympathoexcitation which activates heart function and induces vasoconstriction in the major organs1,2. These cardiovascular responses are necessary to efficiently supply oxygen–rich blood to organs such as skeletal muscles, which have high metabolic demands. Decreased parasympathetic nerve activity during exercise is also involved in the tachycardiac response. However, accumulating evidence suggests that the role of the sympathetic nervous system in regulating heart rate (HR) is large. Adrenaline secretion induced by adrenal sympathoexcitation also contributes to tachycardia but dilates blood vessels of skeletal muscle via activation of β2 adrenergic receptors. This is an important mechanism to maintain high blood flow levels in the active skeletal muscles. The next question relates to how sympathetic outflow is

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centrally regulated during a single bout of exercise. The current understanding of the brain mechanisms underlying sympathoexcitation during exercise involves the following: (i) an ascending neural feedback mechanism from skeletal muscle mechanoreceptors and metaboreceptors \(^3\)\(^4\); and (ii) a feedforward (i.e. central command) mechanism which originate from motor control-related brain areas, such as the insular cortex, hypothalamic and mesencephalic locomotor regions \(^5\)\(^6\). Although the contribution of both mechanisms may depend on exercise type, time, and intensity, each is capable of ‘continuous’ increases in sympathetic nerve activity, and consequently, AP and HR. Although many brain areas are likely involved in regulating hemodynamic responses during exercise, we postulate that the nucleus of the solitary tract (NTS) is one of key brain sites for cardiovascular control during exercise. Please also refer to our recent publication introducing potential brain mechanisms underlying cardiovascular control during exercise \(^7\).

**NTS functions in regulating the cardiovascular system**

The NTS, which is located in the dorsomedial aspect of the medulla oblongata, is innervated by visceral inputs from a large number of peripheral receptors within the gastrointestinal, gustatory, pulmonary/respiratory, and cardiovascular systems, which reflexly affect a wealth of autonomic motor outputs, indicating it a vital component for the homeostasis of autonomic function \(^8\). With regard to the cardiovascular system, the NTS controls AP and HR to maintain cardiovascular homeostasis. The primary cardiovascular reflex mediated by the NTS is the arterial baroreceptor reflex. Arterial baroreceptors are mechanoreceptors that are located in the aortic arch and the carotid sinuses, and stimulated by stretching of the arterial wall when AP increases. Baroreceptor afferent signals are then sent to the NTS, the primary termination site for the afferents. Second-order NTS glutamatergic neurons excite GABAergic inhibitory neurons in the caudal ventrolateral medulla (CVLM) that project and inhibit rostral ventrolateral medulla (RVLM) glutamatergic neurons, thereby decreasing sympathetic preganglionic neuronal outflow (Figure-1) \(^9\). The NTS neurons also excite parasympathetic preganglionic cell bodies located in the nucleus ambiguous. As a result, increased parasympathetic and decreased sympathetic outflows induce bradycardic response, diminished cardiac output, and decreased total peripheral resistance. These responses contribute to normalizing increased AP. Opposite autonomic effects, namely, reduced parasympathetic and increased sympathetic drive, are observed when AP decreases. Thus, the baroreceptor function is required to be modified for continuous increases in sympathetic outflow, AP, and HR under certain physiological conditions such as exercise.

**The NTS is a key brain region in regulating the cardiovascular system during exercise**

As discussed above, the NTS is the central termination site for baroreceptor inputs. Importantly the NTS also receives direct projections from spinal dorsal horn neurons, which transmit afferent inputs from skeletal muscle \(^4\)\(^10\). And moreover, the NTS also receives numerous inputs from other brain areas, including the dorsomedial hypothalamus: DMH or hypothalamic paraventricular nucleus: PVN \(^11\)\(^12\); these networks are considered for candidate pathways of the central command) (Figure-1). Therefore, the NTS is considered to be a central site that integrates the descending and ascending inputs while regulating baroreceptor function during exercise. Indeed, strong expression of the c-fos protein, which is generally used as a marker for neuronal activity, was found in the NTS in response to treadmill running in rats (unpublished data by Waki H.), suggesting that the NTS is likely to be one of the cardiovascular centres where activation of local neuronal networks occurs to modulate the baroreceptor reflex during exercise. Our prediction is that some c-fos positive neurones in the NTS are GABAergic inter–neurones which inhibit the NTS barosensitive neurones (Figure-1). Alternatively, these neurones may be the NTS chemosensitive neurones which directly innervate and excite RVLM sympathetic premotor neurons \(^13\). Thus, the NTS is capable of continually exciting sympathetic premotor neurones located mainly in the RVLM and this may result in sympathoexcitation during exercise. This scenario needs to be
confirmed by further experiments. The next question relates to which mechanisms and brain areas can be involved to control the NTS functions during a single bout of exercise. Our recent findings demonstrate that the posterior hypothalamus - NTS network should be considered for one of the candidate pathways of the central command mechanism.

**Histaminergic system in the NTS**

We performed a genome-wide microarray expression analysis using the NTS tissue from exercise-trained animals (over 10 weeks voluntary wheel running)\(^\text{(14)}\). We screened for genes in the NTS that were differentially expressed between the daily exercised rats and sedentary control rats. Total RNA was extracted from the NTS and Rat Genome Oligo DNA Microarray (Agilent Technolo-

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**Figure–1** Hypothetical models to explain the central mechanisms underlying exercise–induced cardiovascular responses

Main brain regions in the hypothalamus and brainstem where can control the cardiovascular system are shown. The current understanding of the brain mechanisms underlying cardiovascular responses during exercise involves an ascending neural feedback mechanism from skeletal muscle receptors and a central command mechanism which may originate from motor control-related brain areas, such as the insular cortex and hypothalamic locomotor regions (subthalamic nucleus: STN). The descending and ascending signals input to the cardiovascular centres located in the medulla oblongata such as the nucleus of the solitary tract (NTS) and the rostral ventrolateral medulla (RVLM). In these central networks, our findings demonstrate that the tuberomammillary nucleus (TMN) – NTS pathway may have an important role in a central feedforward mechanism underlying especially pressor responses to a single bout of exercise (see the text for more details). Note that solid lines represent the central pathways of the baroreceptor reflex arc. PVN: hypothalamic paraventricular nucleus; DMH: dorsomedial hypothalamus; PAG: periaqueductal gray area; MRN: pallidal raphe nucleus; NA: nucleus ambiguous; CVLM: caudal ventrolateral medulla. Figure modified with permissions from Waki H: Phys Fitness Sports Med, 2012, 1: 253-261.\(^\text{7)}\)
the physiological role of histamine within the CNS is still emerging. It is an important regulator of the sleep–wake cycle, arousal level, learning, pain sensation, stress responses, fluid balance, food intake and body temperature. In addition to these functions, it has been reported that central histamine can regulate the cardiovascular system. Indeed, we found that microinjection of histamine or 2-pyridylethylamine, a H1 receptor specific agonist into the NTS, dose-dependently increased AP and HR. Most importantly, we confirmed that the pressor response induced by the activation of this receptor in the NTS was increased after long-term daily exercise. These findings suggest that the histaminergic system may have an important role in regulating the cardiovascular system during a single bout of exercise and its functional plasticity may be involved in exercise training-induced cardiovascular adaptations. The mechanisms underlying the H1 receptor-mediated inhibition of NTS function in regulating AP and HR still need to be elucidated. Considering that the H1 receptor is a member of the G protein-coupled receptor superfamily and excites neurons in most brain regions through activation of the Gq/11-phospholipase C pathway, histamine in the NTS may activate inhibitory interneurons via H1 receptors, thereby decreasing the excitability of barosensitive neurons in the NTS. The possibility also needs to be considered that the 2nd-order chemosensitive neurons in the NTS are excited by H1 receptors expressed on these neurons and hence, this results in activation of RVLM sympathetic premotor neurons.

Figure 2 Pressor and tachycardiac responses during electrical stimulation of the TMN
(Left) Histidine decarboxylase-positive cells (histaminergic cells) were located specifically in the ventral TMN of the posterior hypothalamic region. This area was electrically stimulated by a microelectrode in anesthetized rats. (Right) Representative recordings illustrating the cardiovascular changes induced by TMN stimulation. Similar to the cardiovascular responses evoked by H1 agonist microinjections into the NTS (see text), pressor and tachycardiac responses were observed.
regions, periaqueductal gray area, medullary raphe (pallidal raphe nucleus) (Figure-1) [4, 7, 10, 11]. Based on our recent findings, we propose that the tuberomammillary nucleus (TMN) of the posterior hypothalamus may also be an important brain site in exercise-induced cardiovascular responses. The TMN is anatomically located in the hypothalamic defense area, and we confirmed that histamine-immunoreactive neuronal cell bodies are found exclusively in this nucleus as previously reported (Figure-2 left-top) [15, 16, 28, 29]. However, immunoreactive fibers are observed throughout the cerebral cortex and in parts of other brain regions including the olfactory bulb and tubercle, amygdala, substantia nigra, parabrachial nucleus and the NTS [11, 17, 29]. Since central histamine is known as an important regulator of arousal level, it is conceivable that the histaminergic system is activated during exercise (i.e. high-arousal condition). We therefore electrically stimulated the TMN in anesthetized rats, and similar to the cardiovascular responses evoked by H1 agonist microinjections into the NTS, pressor and tachycardiac responses were observed (Figure-2 left-bottom and right) [30]. More importantly the pressor responses were partially inhibited by cetirizine, a H1 receptor antagonist, microinjected into the NTS whereas we failed to see the inhibitory effects on the HR responses [30]. As previously reported, we also histologically confirmed that the TMN neurons directly project to the NTS by using a retrograde tracer, Fluoro-Gold [30]. Taken together, these findings demonstrate that the TMN-NTS pathway is likely involved in the central pressure responses presumably under high arousal phase. Our supposition is that the TMN-NTS pathway has an important role especially in a central feed forward mechanism (central command) underlying pressor responses to a single bout of exercise, although this hypothesis needs to be tested in the future.

Conclusions

During a single bout of exercise, neuronal signals from the central command, mediated by the hypothalamic nuclei including the TMN, and those from the muscle receptors are integrated within the NTS, resulting in sympathoexcitation in most sympathetic fibers, and hence AP and HR increases. This may only partially explain the mechanisms underlying cardiovascular responses during exercise. Since maintaining cardiovascular homeostasis is essential for high exercise performance, further investigations will be required to fully understand the aspects of the central regulatory mechanisms of the cardiovascular system during exercise.

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References


