Central mechanisms of cardiovascular regulation during exercise: Integrative functions of the nucleus of the solitary tract

Hidefumi Waki

Department of Physiology, Wakayama Medical University School of Medicine, 811-1 Kimiidera, Wakayama 641-8509, Japan

Received: April 17, 2012 / Accepted: June 7, 2012

Abstract Generally, a single bout of exercise induces a moderate increase in arterial pressure (AP) with marked tachycardia as a result of sympathoexcitation which induces vasoconstriction in the major organs, but not in skeletal muscles, and activates heart function. In this review, the potential brain mechanisms underlying cardiovascular regulation during exercise are introduced, with a focus on the functions of the nucleus of the solitary tract (NTS), which is the central termination site of baroreceptor inputs. During a single bout of exercise, neuronal signals from the central command, mediated by the hypothalamus, as well as those from the muscle receptors, are directly or indirectly projected to the NTS and rostral ventrolateral medulla (RVLM). The signals to the RVLM activate sympathetic premotor neurons that, in turn, induce pressor and tachycardiac responses. However, in the absence of resetting of the baroreceptor reflex to a higher pressure range, sympathoexcitation would be dampened and parasympathetic nerves would be excited by heightened levels of baroreceptor inputs, resulting in the attenuation of continuous increases in AP and heart rate. The GABAergic inter-neurons within the NTS may be involved in baroreceptor reflex resetting by limiting the degree of excitation of barosensitive NTS neurons, and thus are capable of 'continuous' increases in sympathetic nerve activity. Among the central command mechanisms, the dorsomedial hypothalamus, hypothalamic paraventricular nucleus, and tuberomammillary nucleus of the posterior hypothalamus may be involved in the GABA-mediated inhibition of NTS functions. Although the recent findings of the central regulatory mechanisms are remarkable, they may provide only a partial explanation of the mechanisms. Since maintaining cardiovascular homeostasis is essential for high exercise performance, further investigations will be required to clarify all aspects of the central regulatory mechanisms underlying cardiovascular responses during exercise.

Keywords : nucleus of the solitary tract (NTS), arterial pressure, baroreceptor reflex, exercise, cardiovascular centers, hypothalamus

Introduction

One of the major mechanisms underlying cardiovascular regulation during a single bout of exercise is an increase in sympathetic nerve activity. Although the central mechanisms of sympathoexcitation are still considered a black box, findings increasingly reveal partial but novel central pathways involved in the mechanisms. The nuclei located in the hypothalamus and brainstem are thought to be involved in these pathways. Among them, the nucleus of the solitary tract (NTS) in the medulla oblongata has been considered a key site in the brain. In this review, the basic functions of the NTS with respect to regulating the cardiovascular system are introduced. Then, the potential mechanisms underlying cardiovascular regulation during a single bout of exercise are discussed, with a focus on NTS functions.

Cardiovascular regulation by the NTS

The NTS lies within the dorsomedial aspect of the medulla oblongata. It is innervated by visceral inputs from a host of peripheral receptors located within the gastrointestinal, gustatory, cardiovascular, and pulmonary/respiratory systems, which reflexly affect a wealth of autonomic motor outputs, indicating it a vital component for the homeostasis of autonomic function¹⁾. With regard to the cardiovascular system, the NTS reflexly controls arterial pressure (AP) and heart rate (HR) to maintain cardiovascular homeostasis; this brain nucleus also mediates feedforward regulation in the cardiovascular system in response to a variety of mental and physical stressors.

The primary cardiovascular reflex mediated by the NTS is the arterial baroreceptor reflex. Arterial baroreceptors are located in the aortic arch and the carotid sinuses of the internal carotid arteries. Baroreceptors are mechanoreceptors that are 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 parasympathetic preganglionic cell bodies located in the nucleus ambiguus and GABAergic inhibitory neurons in the caudal ventrolateral medulla (CVLM) that project and inhibit rostral ventrolateral medulla (RVLM) glutamatergic neurons, thereby decreasing sympathetic preganglionic neuronal outflow²⁾. As a result, increased parasympathetic and decreased sympathetic outflows induce a marked 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.

The arterial baroreceptor reflex function exhibits dynamic characteristics in response to mental and physical stress. The NTS receives numerous inputs from other brain sites including the amygdaloid complex, dorsomedial hypothalamus (DMH), hypothalamic paraventricular nucleus (PVN), periaqueductal gray area (PAG), and medullary raphe. The NTS also receives direct projections from spinal dorsal horn neurons which transmit inputs from the skeletal muscle receptors to the NTS³⁾. These descending and ascending inputs presynaptically or postsynaptically modulate the NTS barosensitive neurons. Therefore, the NTS is considered a central site which integrates multiple information sources, consequently affecting baroreceptor reflex functions. The dynamic characteristics of the baroreceptor reflex function can be shown as changes in the reflex gain (or sensitivity) and shift of the set point of AP, a process known as “resetting”, in the baroreceptor reflex function curve, where the X-axis represents AP, and Y-axis represents HR or sympathetic nerve activity (Fig.1). Changes in the reflex gain represent changes in the stability of AP, whereas resetting indicates a change in the basal level of AP and/or HR (or sympathetic nerve activity) resulting in normal efficient reflex function around the new pressure level. Thus, the integrative functions of the NTS are fundamental to modulate the baroreceptor reflex, acutely or chronically, and play important roles in regulating cardiovascular homeostasis during mental and physical stress. In fact, its destruction is lethal as it induces cardiovascular disorder characterized as augmented fluctuation of AP at a high level⁴⁻⁹⁾.

Outline of hemodynamics during exercise and its regulatory mechanisms

Generally, a single bout of exercise induces a moderate increase in AP with marked tachycardia as a result of sympathoexcitation which induces vasoconstriction in the major organs (but not in skeletal muscles) and activates heart function^{10,11)}. Although the pattern of cardiovascu-

lar responses is not uniform and is affected by intensity, time, and types of exercise, only the type of exercise that induces pressor and tachycardiac responses shall be discussed in this review. These cardiovascular responses are necessary to efficiently adjust blood supply to organs such as skeletal muscles, which have high metabolic demands. Decreased parasympathetic nerve activity is also involved in the tachycardiac response. However, accumulating evidence suggests that the role of the sympathetic nervous system in regulating HR during exercise is large. The increase in adrenaline secretion induced by adrenal sympathoexcitation also contributes to tachycardia and facilitates vasodilatation in blood vessels of skeletal muscle via activation of β_2 adrenergic receptors. Moreover, vascular resistance in the skeletal muscles may be reduced by activation of sympathetic cholinergic vasodilator fibers¹²⁾. Thus, overall cardiovascular regulation during a single bout of exercise is the result of sympathoexcitation. However, it should be noted that sympathetic noradrenergic vasomotor nerves in skeletal muscles are indeed inhibited during exercise, which contributes to an increase in blood flow in active skeletal muscles. Since the central pathways for regulating sympathetic noradrenergic drive to the skeletal muscles are extremely specific, the central pathways which contribute to sympathoexcitation are the focus of this review, unless specified otherwise.

The next question relates to how sympathetic outflow

Fig. 1 Dynamic characteristics of the arterial baroreceptor reflex. The graph shows the baroreceptor reflex function curve, where the X-axis represents arterial pressure (AP) and the Y-axis represents heart rate (HR) or sympathetic nerve activity. The nucleus of the solitary tract (NTS) regulates the cardiovascular system by modulating the baroreceptor reflex functions. The dynamic functions of the baroreceptor reflex can be shown as changes in the reflex gain (or sensitivity) and shift in set points of AP, a process known as “resetting”. If the curve changes from A to B, the set point (○) exhibits an upward and rightward shift, demonstrating that both AP and sympathetic nerve activity (or HR) have increased. If the curve changes from A to C, the reflex gain appears to decrease with upward and rightward resetting, demonstrating increased fluctuation of AP at a high-pressure level.

Multiple brain areas are predicted to be involved in

feedforward and/or feedback mechanisms in regulating the cardiovascular system during exercise. In particular, numerous candidate brain sites are expected to be involved in the central command mechanism. Such brain areas are the motor cortex, hypothalamic locomotor regions (subthalamic nucleus), perifornical region in the hypothalamus, DMH, PVN, mesencephalic locomotor regions, PAG, medullary raphe (Pallidal raphe nucleus), and the central nuclei of the baroreceptor reflex (CVLM, RVLM, and NTS). The potential participation of these nuclei has mainly been identified by animal studies under anesthetic or in unanesthetized decerebrate *in situ* perfused brainstem preparations^{3,21}). To correctly understand the central pathways underlying central command regulation, experiments using conscious animals exposed to exercise are required. Even if this type of experiment were performed, it would still be difficult to identify the details of the central pathways since these brain sites exhibit reciprocal projections. In the hypothalamus, especially, the candidate nuclei which participate in exercise-induced cardiovascular regulation are adjacent to each other and difficult to distinguish. Moreover, as discussed later, cardiovascular responses during exercise may be partially mediated by central regulatory mechanisms in alerting response; thus, identifying the descending pathways involved in only exercise-associated central events is extremely difficult. In this regard, since the major cardiovascular centers, which are responsible for the feedback mechanisms mediated by muscle receptors, are predicted to be located mostly within the medulla oblongata, and muscle receptors/afferents can be mechanically/electrically stimulated under anesthetic conditions, thus simplifying the study of feedback regulation. However, it should be noted that artificial stimulation of muscle receptors/afferents cannot perfectly simulate actual firing patterns in response to volitional

During a single bout of exercise, neuronal signals from the central command that may originate from the locomotor brain centers and are mediated by the hypothalamic nuclei (i), as well as those from the muscle receptors (ii), are directly or indirectly projected to the NTS and RVLM. The signals to the RVLM activate sympathetic premotor neurons (arrows in gray and broken lines). However, to maintain a high level of sympathetic nerve activity, the NTS second-order barosensitive neurons need to be inhibited to evoke resetting of the baroreceptor reflex to a higher pressure range (black and white arrows). This may explain the mechanisms underlying continuous increases in both AP and HR during a single bout of exercise.

movement. Considering these limitations, the author summarizes the present ideas of potential central mechanisms regulating the cardiovascular system during a single bout of exercise with a focus on the role of NTS functions.

1. Central mechanisms mediated by the hypothalamic-brainstem system: implications for the central command mechanism

In the hypothalamus, there is an area that induces increases in AP, HR, sympathetic nerve activity (but not in skeletal muscles), and muscle blood flow. This specific brain site is called “the hypothalamic defense area” and is known to produce cardiovascular responses to mental stress (i.e., alerting/defense response)²². This hypothalamic area includes the DMH, perifornical region of the hypothalamus, and posterior hypothalamus. Electrical stimulation in the subthalamic nucleus located in the posterior hypothalamus is known to evoke locomotor activity; therefore, this nucleus is often referred to as the hypothalamic locomotor region²³. Since the hypothalamic nuclei are very closely located together, it is not easy to identify which particular nucleus is responsible for regulating autonomic cardiovascular events through electrical stimulation. However, accumulating evidence obtained by chemical stimulation techniques (i.e., drug microinjections) has revealed functional roles in each nucleus in the hypothalamus^{24,25}. Although the central pathways of the central command and those involved in the alerting response are substantially different - as the first-order nucleus/nuclei are thought to be different, it is thought that they partially/mostly overlap each other in the hypothalamus and brainstem. The important note is that the hypothalamic pathways involved in the alerting response under conditioned stress, which elicits a certain response through memory, are different from those under unconditioned stress, which produces an instinctive response²⁶. In response to conditioned stress, the perifornical region in the hypothalamus likely takes part in regulating the cardiovascular system, and the induced pressor response is thought to be mediated by activation of sympathetic premotor neurons located in the A5 or PVN, but not in the RVLM²⁷. Moreover, stimulation of the perifornical region in the hypothalamus enables induction of baroreceptor reflex resetting to a high-pressure range by inhibiting the NTS neurons directly, or through mediation with the PAG neurons²⁴. On the other hand, DMH is considered to be important for cardiovascular responses to unconditioned stress. The information from DMH diverges to the RVLM, NTS, and pallidal raphe nucleus, inducing specific cardiovascular responses¹⁷. Considering the case of actual exercise, the alerting response is thought to be intermingled; however, substantial cardiovascular responses are evoked by the central command that could be an instinctive control system. In this regard, DMH is also likely to be a key brain region for the central command-induced cardiovascular responses. The first-order nucleus

(or nuclei) in the central command remain unknown. The anterior cingulate cortex, insular cortex, and hypothalamic locomotor regions have been suggested as the candidate brain areas. Dampney et al. suggested that the signal from the higher center(s) inputs to the DMH and that the DMH neurons are capable of increasing vasomotor sympathetic nerve activity through activation of sympathetic premotor neurons in the RVLM. They also suggested cardiac sympathetic nerve activity through activation of sympathetic premotor neurons in the pallidal raphe nucleus^{17,28}. In addition, stimulation of the DMH neurons enables induction of baroreceptor reflex resetting to a higher pressure range by modulating the NTS neurons. The GABAergic inter-neurons within the NTS may be involved in the modulatory effects and limit the degree of excitation of barosensitive NTS neurons. It is suggested that this mechanism induces resetting of the baroreceptor reflex while preserving reflex gain. Thus, excitation of DMH neurons enables continuous increases of both AP and HR (Fig. 3). In the alerting response, midbrain PAG is also known to be involved in cardiovascular responses. Although the PAG and DMH exhibit reciprocal projections, the significant roles of the ascending pathway from the PAG to the DMH have been implicated in the alerting response^{17,29}. Most importantly, recent studies measuring local field potential of the PAG in humans suggest that the PAG is also involved, via the central command, in exercise-induced cardiovascular responses³⁰. Sarkar et al suggested that the PAG may exert integrative functions from other inputs, but not likely one of the first-order nuclei³⁰. As mentioned later, the PAG-DMH pathway may be involved in the central command and have an important role in regulating the cardiovascular system during a single bout of exercise (Fig. 3).

The author recently found 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 histamine-immunoreactive neuronal cell bodies are found exclusively in this nucleus. It was found that daily exercise altered the expression levels of some NTS genes in rats, which are associated with neuroactive ligand-receptor interactions^{31,32}. One of these genes was histamine receptor H₁, suggesting that the histaminergic system within the NTS is involved in exercise-induced physiological events³¹. Since central histamine is an important regulator of arousal level, it is conceivable that the histaminergic system is activated during exercise (i.e., high arousal level). It was further confirmed that activation of this receptor induces pressor and tachycardiac responses at the level of the NTS³³, and that these responses exhibit functional plasticity after long-term daily exercise³². The author postulates that the histaminergic system in the TMN-NTS pathways is involved in the central command and has an important role in regulating the cardiovascular system during a single

Fig. 3 Hypothetical models to explain the central mechanisms underlying cardiovascular control by the central command during exercise

Both solid and double lines represent the central pathways of the baroreceptor reflex arc. As a matter of convenience, the pathways shown by solid lines represent the central circuit that responds to acute changes in the baroreceptor inputs (i.e., changes in AP), but is not able to respond when the input changes have reached a steady state. This indicates that this circuit exerts reflex control with a certain gain at any set point of AP. On the other hand, the pathways shown by double lines represent the central circuit which responds to slow changes in the baroreceptor inputs and is able to respond even when the input changes have reached a steady state, indicating that this circuit modulates the set points of AP.

The dorsomedial hypothalamus (DMH) located in the hypothalamic defense area is likely one of the key brain regions for exercise-induced cardiovascular responses evoked by the central command. A signal from the higher center(s) is transmitted to the DMH, and the DMH neurons are capable of increasing vasomotor sympathetic nerve activity through activation of sympathetic premotor neurons in the rostral ventrolateral medulla (RVLM) and cardiac sympathetic nerve activity through activation of sympathetic premotor neurons in the pallidal raphe nucleus (MRN). These pathways are fundamental mechanisms for increasing both AP and HR (pathways indicated by broken lines-i). However, in the absence of resetting the baroreceptor reflex, the sympathoexcitation would be dampened (and parasympathetic nerves would be excited) by heightened levels of baroreceptor inputs, resulting in the attenuation of continuous increases in AP and HR (pathways indicated by double lines). Stimulation of the DMH neurons enables resetting of the baroreceptor reflex to a higher pressure range by modulating the NTS neurons. The GABAergic inter-neurons within the NTS may be involved in the modulatory effects and limit the degree of excitation of barosensitive NTS neurons (pathways indicated by broken lines-ii). In addition, vasopressinergic inputs from the hypothalamic paraventricular nucleus (PVN) to the NTS and histaminergic inputs from the tuberomammillary nucleus (TMN) to the NTS are also capable of resetting reflex control toward higher AP values (pathways indicated by broken lines-iii). Moreover, the periaqueductal gray area (PAG), hypothalamic locomotor regions (subthalamic nucleus: STN), and cerebral cortex (such as anterior cingulate cortex and insular cortex) may also be involved in the central command. These hypothetical neuronal circuits explain the mechanisms underlying sympathoexcitation in most sympathetic fibers as well as resetting of the baroreceptor reflex, which evokes continuous increases in both AP and HR during a single bout of exercise. It should be noted that the gain of the baroreceptor reflex remains unchanged during this type of exercise (pathways indicated by solid lines are not affected.). NA: nucleus ambiguus, CVLM: caudal ventrolateral medulla

bout of exercise (Fig. 3). This hypothesis will be tested in the future.

In addition to the central pathways between the hypothalamic defense area and the NTS, Michelini and Stern¹⁸⁾ have reported that vasopressinergic inputs from the PVN to the NTS are also capable of resetting the reflex control toward high pressure and HR values, facilitating the appearance of exercise that induces an increase in AP and tachycardia^{18,34)}. They postulated that this pathway is also involved in the central command during a single bout of exercise (Fig. 3). Another interesting note is that the PVN magnocellular and parvocellular neurosecretory neurons receive inputs from the NTS noradrenergic neurons, and this ascending pathway enables indirect transmission of peripheral information of the baroreceptors to the PVN. The reciprocal interconnectivity between the NTS and PVN may act as a prompt feedback loop for cardiovascular adjustments during a single bout of exercise. Although the source of descending pathways to the PVN remains unknown, the PVN also receives the DMH neurons within the hypothalamus, suggesting that PVN-evoked cardiovascular responses may also be a part of DMH-induced cardiovascular responses during a single bout of exercise.

The central mechanisms, in regulating the cardiovascular system described above, explain the increase in AP and HR during exercise. Now, questions arise as to how peripheral vascular resistance in skeletal muscles can decrease during exercise. As shown earlier, the increase of adrenaline secretion induced by adrenal sympathoexcitation facilitates vasodilatation in skeletal muscle blood vessels via activation of β_2 adrenergic receptors. Vascular resistance in the skeletal muscles may also be reduced by activation of sympathetic cholinergic vasodilator fibers. Thus, one of the mechanisms underlying the reduced peripheral vascular resistance in skeletal muscles during a single bout of exercise is sympathoexcitation. However, sympathetic noradrenergic vasomotor neurons in skeletal muscles are indeed inhibited during exercise, which also contributes to an increase in blood flow in active skeletal muscles. In this regard, it is known that the pattern of sympathetic outflow in response to different types of mental and physical stress is organ specific. There have been some reports exploring the potential mechanisms on organ-specific sympathetic controls. One idea is that the prinergeric receptors in the NTS may play a key role^{35,36)}. The prinergeric receptors include adenosine receptors A_1 and A_{2A} , and ATP receptors such as P2X. The pattern of sympathetic outflow depends on which receptor subtypes expressed in the NTS are stimulated³⁵⁾. The reason for this may be that the NTS also contains excitatory neurons which directly innervate RVLM neurons (note that this pathway is not involved in the central baroreceptor reflex arc), enabling an increase in sympathetic premotor neurons in the RVLM. Different subtypes of the purinergic receptor expressed on the NTS neural dendrites and terminals may trigger different central pathways (i.e.,

NTS-CVLM-RVLM or NTS-RVLM). Therefore, the NTS may be an important brain site for exerting organ-specific sympathetic controls; although confirmation is required. Another potential mechanism underlying organ-specific sympathetic controls may involve the PAG. It has been known that cardiovascular responses induced by PAG stimulation are extremely site specific. Stimulation of one area induces hypertension, whereas that of another area exerts an increase in skeletal muscle blood flow³⁷⁾. These responses are known to be mediated by the RVLM. All told, the PAG-DMH-RVLM or PAG-RVLM pathway may also be involved in sympathoinhibition in skeletal muscles during a single bout of exercise.

Finally, it needs to be mentioned that the mesencephalic locomotor regions may also be involved in cardiovascular regulation, through the central command, during exercise³⁸⁾. Electrical stimulation in this brain area evokes similar cardiovascular actions as electrical stimulation in the hypothalamic locomotor regions. The central pathways mediating the mesencephalic locomotor regions remain unknown; however, the author suspects that the cardiovascular actions are at least mediated by the NTS since the resetting of the baroreceptor reflex to a higher AP range has also been found during stimulation of this brain area³⁸⁾.

2. Central mechanisms mediated by skeletal muscle receptors: implication for the feedback mechanism

A part of the central mechanisms, regulating the cardiovascular system during a single bout of exercise, has been explained by the feedback mechanism mediated by muscle afferents. For details, refer to the review by Potts³⁾ who postulated that the NTS is the first medullary region where a potential central interaction between baroreceptor and somatosensory receptor inputs can occur, since the baroreceptor afferents and some spinal dorsal horn neurons, which transmit inputs from the skeletal muscle receptors, project to and synapse within the NTS. Among the feedback mechanisms, inputs from muscle contraction-sensitive A δ and C fibers are presumably involved in direct excitation of sympathetic premotor neurons in the RVLM, which in turn induces pressor and tachycardiac responses. On the other hand, these fibers may inhibit the baroreceptor reflex function through GABA release within the caudal part of the NTS^{3,21)}. This somato-GABAergic mechanism may shunt second-order barosensitive neurons, which are heightened during exercise as a result of high-pressure, resulting in functional resetting of the baroreceptor sympathetic reflex while retaining overall sensitivity (Fig. 4)³⁾. This mechanism enables an increase in both AP and HR during a single bout of exercise³⁾.

Conclusions

During a single bout of exercise, neuronal signals from the central command, mediated by the hypothalamic nu-

Fig. 4 Hypothetical models for explaining the central mechanisms underlying cardiovascular control by the skeletal muscle receptors during exercise

Both solid and double lines represent the central pathways of the baroreceptor reflex arc (see Fig. 3). Inputs from muscle contraction-sensitive A δ and C fibers presumably stimulate sympathetic premotor neurons in the RVLM that, in turn, induce pressor and tachycardiac responses (pathways indicated by broken lines i). However, in the absence of resetting of the baroreceptor reflex, sympathoexcitation would be dampened (and parasympathetic nerves would be excited) by heightened levels of baroreceptor inputs, resulting in an attenuation of the continuous increases in AP and HR (pathways indicated by double lines). The signals from the muscle afferents may be transmitted to the NTS and inhibit baroreceptor reflex function by GABA release within the NTS^{3,21}). This somato-GABAergic mechanism may shunt second-order barosensitive neurons that are activated during exercise as a result of high pressure (pathways indicated by broken lines ii). With the central command, this feedback mechanism induces sympathoexcitation in most sympathetic fibers (but not in skeletal muscles), and resetting of the baroreceptor reflex, which evokes continuous increases in both AP and HR during a single bout of exercise. It should be noted that the gain of baroreceptor reflex remains unchanged during this type of exercise (pathways indicated by solid lines are not affected.).

clei and those from the muscle receptors, are integrated within the RVLM and NTS, resulting in sympathoexcitation in most sympathetic fibers and resetting of the baroreceptor reflex. The latter may explain the mechanisms underlying continuous increases in both AP and HR during a single bout of exercise. Although the recent findings of the central regulatory mechanisms are remarkable, it may only partially explain the mechanisms. Since maintaining cardiovascular homeostasis is essential for high exercise performance, and consequently, is a fundamental physiological process in both daily exercise for health and fitness, and for athletes, further investigations will be required to fully clarify the aspects of the central regulatory mechanisms underlying cardiovascular responses during a single bout of exercise.

Acknowledgements

The author's work described in this review was financially supported by the Japan Society for the Promotion of Science (21300253) and the Takeda Science Foundation.

References

- 1) Barraco IRA. 1994. Nucleus of the Solitary Tract. CRC Press Inc, Boca Raton, Ann Arbor, London, Tokyo.
- 2) Sapru HN. 2004. Neurotransmitters in the nucleus tractus solitarius mediating cardiovascular function. *In: Neural mechanisms of cardiovascular regulation*. (Dun NJ, Machado BH, Pilowsky PM, eds.), 4: 81-98, Kluwer Academic Publishers, Boston.
- 3) Potts JT. 2006. Inhibitory neurotransmission in the nucleus tractus solitarius: implications for baroreflex resetting during

- exercise. *Exp Physiol* 91: 59-72.
- 4) Doba N, Reis DJ. 1973. Acute fulminating neurogenic hypertension produced by brainstem lesions in the rat. *Circ Res* 32: 584-593.
 - 5) Talman WT, Perrone MH, Reis DJ. 1981. Acute hypertension after the local injection of kainic acid into the nucleus tractus solitarii of rats. *Circ Res* 48: 292-298.
 - 6) Machado, B.H. 2001. Neurotransmission of the cardiovascular reflexes in the nucleus tractus solitarii of awake rats. *Ann N Y Acad Sci* 940: 179-196.
 - 7) Thrasher TN. 2002. Unloading arterial baroreceptors causes neurogenic hypertension. *Am J Physiol Regul Integr Comp Physiol* 282: R1044-R1053.
 - 8) Thrasher TN. 2006. Arterial baroreceptor input contributes to long-term control of blood pressure. *Curr Hypertens Rep* 8: 249-254.
 - 9) Waki H, Gouraud SS, Maeda M, Paton JF. 2010. Evidence of specific inflammatory condition in nucleus tractus solitarii of spontaneously hypertensive rats. *Exp Physiol* 95: 595-600.
 - 10) Ludbrook J, Graham WF. 1985. Circulatory responses to onset of exercise: role of arterial and cardiac baroreflexes. *Am J Physiol Heart Circ Physiol* 248: H457-H467.
 - 11) Waki H, Kasparov S, Katahira K, Shimizu T, Murphy D, Paton JF. 2003. Dynamic exercise attenuates spontaneous baroreceptor reflex sensitivity in conscious rats. *Exp Physiol* 88: 517-526.
 - 12) Komine H, Matsukawa K, Tsuchimochi H, Nakamoto T, Murata J. 2008. Sympathetic cholinergic nerve contributes to increased muscle blood flow at the onset of voluntary static exercise in conscious cats. *Am J Physiol Regul Integr Comp Physiol* 295: R1251-R1262.
 - 13) Kaufman MP. 2012. The exercise pressor reflex in animals. *Exp Physiol* 97: 51-58.
 - 14) Goodwin GM, McCloskey DI, Mitchell JH. 1972. Cardiovascular and respiratory responses to changes in central command during isometric exercise at constant muscle tension. *J Physiol* 226: 173-190.
 - 15) Matsukawa K. 2012. Central command: control of cardiac sympathetic and vagal efferent nerve activity and the arterial baroreflex during spontaneous motor behaviour in animals. *Exp Physiol* 97: 20-28.
 - 16) Mueller PJ, Hasser EM. 2005. Putative role of the NTS in alterations in neural control of the circulation following exercise training in rats. *Am J Physiol Regul Integr Comp Physiol* 290: R383-R392.
 - 17) Dampney RA, Horiuchi J, McDowall LM. 2008. Hypothalamic mechanisms coordinating cardiorespiratory function during exercise and defensive behaviour. *Auton Neurosci* 142: 3-10.
 - 18) Michelini LC, Stern JE. 2009. Exercise-induced neuronal plasticity in central autonomic networks: role in cardiovascular control. *Exp Physiol* 94: 947-960.
 - 19) Miki K, Yoshimoto M, Tanimizu M. 2003. Acute shifts of baroreflex control of renal sympathetic nerve activity induced by treadmill exercise in rats. *J Physiol* 548: 313-322.
 - 20) Ogoh S, Fadel PJ, Nissen P, Jans Ø, Selmer C, Secher NH, Raven PB. 2003. Baroreflex-mediated changes in cardiac output and vascular conductance in response to alterations in carotid sinus pressure during exercise in humans. *J Physiol* 550: 317-324.
 - 21) Potts JT, Paton JF, Mitchell JH, Garry MG, Kline G, Angue-
lov PT, Lee SM. 2003. Contraction-sensitive skeletal muscle afferents inhibit arterial baroreceptor signalling in the nucleus of the solitary tract: role of intrinsic GABA interneurons. *Neuroscience* 119: 201-214.
 - 22) Hilton SM, Redfern WS. 1986. A search for brain stem cell groups integrating the defence reaction in the rat. *J Physiol* 378: 213-228.
 - 23) Waldrop TG, Bauer RM, Iwamoto GA. 1988. Microinjection of GABA antagonists into the posterior hypothalamus elicits locomotor activity and a cardiorespiratory activation. *Brain Res* 444: 84-94.
 - 24) McDowall LM, Horiuchi J, Killinger S, Dampney RA. 2006. Modulation of the baroreceptor reflex by the dorsomedial hypothalamic nucleus and perifornical area. *Am J Physiol Regul Integr Comp Physiol* 290: R1020-R1026.
 - 25) McDowall LM, Horiuchi J, Dampney RA. 2007. Effects of disinhibition of neurons in the dorsomedial hypothalamus on central respiratory drive. *Am J Physiol Regul Integr Comp Physiol* 293: R1728-R1735.
 - 26) Furlong T, Carrive P. 2007. Neurotoxic lesions centered on the perifornical hypothalamus abolish the cardiovascular and behavioral responses of conditioned fear to context but not of restraint. *Brain Res* 1128: 107-119.
 - 27) Carrive P, Gorissen M. 2008. Premotor sympathetic neurons of conditioned fear in the rat. *Eur J Neurosci* 28: 428-446.
 - 28) Zaretsky DV, Zaretskaia MV, Samuels BC, Cluxton LK, DiMicco JA. 2003. Microinjection of muscimol into raphe pallidus suppresses tachycardia associated with air stress in conscious rats. *J Physiol* 546: 243-250.
 - 29) Horiuchi J, McDowall LM, Dampney RA. 2009. Vasomotor and respiratory responses evoked from the dorsolateral periaqueductal grey are mediated by the dorsomedial hypothalamus. *J Physiol* 587: 5149-5162.
 - 30) Basnayake SD, Green AL, Paterson DJ. 2012. Mapping the Central Neurocircuitry that Integrates the Cardiovascular Response to Exercise in Humans. *Exp Physiol* 97:29-38.
 - 31) Waki H, Gouraud S, Bhuiyan M., Takagishi M, Kohsaka A, Maeda M. 2011. Daily exercise alters molecular characteristics in the nucleus tractus solitarii of rats –Brain mechanisms underlying exercise-induced cardiovascular adaptation? *J Physiol Sci* 61: S196.
 - 32) Waki H, Gouraud S, Bhuiyan M., Takagishi M, Kohsaka A, Maeda M. 2012. Neuroplasticity of histaminergic system in the nucleus tractus solitarii is involved in exercise-induced cardiovascular adaptations. *J Physiol Sci* 62: S113.
 - 33) Bhuiyan ME, Waki H, Gouraud SS, Takagishi M, Kohsaka A, Maeda M. 2011. Histamine receptor H1 in the nucleus tractus solitarii regulates arterial pressure and heart rate in rats. *Am J Physiol Heart Circ Physiol* 301: H523-H529.
 - 34) Dufloth DL, Morris M, Michelini LC. 1997. Modulation of exercise tachycardia by vasopressin in the nucleus tractus solitarii. *Am J Physiol Regul Integr Comp Physiol* 273: R1271-R1282.
 - 35) Scislo TJ, Kitchen AM, Augustyniak RA, O'Leary DS. 2001. Differential patterns of sympathetic responses to selective stimulation of nucleus tractus solitarius purinergic receptor subtypes. *Clin Exp Pharmacol Physiol* 28: 120-124.
 - 36) Barraco RA, O'Leary DS, Ergene E, Scislo TJ. 1996. Activation of purinergic receptor subtypes in the nucleus tractus solitarius elicits specific regional vascular response patterns. *J Auton Nerv Syst* 59: 113-24.

- 37) Bandler R, Shipley MT. 1994. Columnar organization in the midbrain periaqueductal gray: modules for emotional expression? *Trends Neurosci* 17: 379-389.
- 38) McIlveen SA, Hayes SG, Kaufman MP. 2001. Both central command and exercise pressor reflex reset carotid sinus baroreflex. *Am J Physiol Heart Circ Physiol* 280: H1454-463.