Central mechanisms underlying anti-hypertensive effects of exercise training

Hidefumi Waki1*, Miwa Takagishi2 and Sabine S Gouraud3

1 Department of Physiology, Graduate School of Health and Sports Science, Juntendo University, 1-1 Hirakagakuen-dai, Inzai-shi, Chiba 270-1695, Japan
2 Department of Therapeutic Health Promotion, Kansai University of Health Sciences, 2-11-1 Wakaba, Kumatori-cho, Sennan-gun, Osaka 590-0482, Japan
3 Department of Physiology, Wakayama Medical University School of Medicine, 811-1 Kimiidera, Wakayama 641-8509, Japan

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Abstract  Neurogenic hypertension, the primary form of essential hypertension, is one of the most common diseases worldwide. Hypertension is a risk factor for many cardiovascular diseases such as heart attacks and stroke; therefore, it is crucial to maintain arterial blood pressure (BP) within the normal range. Regular aerobic exercise at moderate intensities can lower basal BP, and is a recommended therapy to prevent or improve primary hypertension. However, the mechanisms underlying the anti-hypertensive effects of exercise remain unknown. In this review, we discuss the mechanisms for the anti-hypertensive effects of exercise training/therapy that are hypothesised from recent findings, including our own. In particular, we discuss the nucleus of the solitary tract (NTS) of the brainstem, which is involved in mechanisms underlying the manifestation of neurogenic hypertension. Moreover, the NTS may also be involved in the anti-hypertensive effects of exercise training. However, exercise training does not seem to improve causative genetic factors for neurogenic hypertension in the NTS. Nevertheless, exercise training may affect other mechanisms responsible for neuroactive ligand-receptor interactions within the NTS, which also regulate BP homeostasis. We hope this review will further enhance research in this and promote exercise habits that help delay or even prevent the progression of essential hypertension.

Keywords : hypertension, exercise, nucleus of the solitary tract, cardiovascular center, baroreceptor reflex

Introduction

Essential hypertension (EH) affects one in three adults. Although it is idiopathic, it is accepted as a complex polygenic trait with underlying genetic components. Because EH is a risk factor for other cardiovascular diseases such as heart attacks and stroke, it is crucial to maintain normal arterial blood pressure (BP). Regular aerobic exercise at moderate intensities can lower basal BP levels in some forms of EH and prevent the progression of hypertension1-3. Since the discovery of the benefits of exercise training for hypertension, studies have focused on the mechanisms underlying how exercise produces anti-hypertensive effects; however, most of them remain unknown. One reason for this uncertainty may be that these anti-hypertensive effects may involve complex polygenic factors. However, accumulating evidence, including our own, suggests that brain areas controlling sympathetic nervous system activity are involved in mechanisms for both the manifestation of EH and the therapeutic anti-hypertensive effects of exercise training. In this review, we focus on the current understating of the central mechanisms that prevent or improve EH after exercise training/therapy.

Exercise training in hypertension

It is generally accepted that daily aerobic exercise prevents hypertension in pre-hypertensive subjects and even reduces BP levels in high-normal (130-139 mmHg in systolic pressure or 85-89 mmHg in diastolic pressure) and Stage 1 hypertension (140-159 mmHg in systolic pressure or 90-99 mmHg in diastolic pressure) in EH. Indeed, the World Health Organisation (WHO), International Society of Hypertension (ISH) and American College of Sports Medicine (ACSM) recommend daily exercise to obtain anti-hypertensive effects1-2. Japanese organisations such as the Ministry of Health, Labour and Welfare, the Japan Medical Association (JMA) and the Japanese Society of Hypertension (JSH) also promote regular exercise4.
The recommended exercise programmes vary among organisations; however, moderate daily aerobic exercise is required for anti-hypertensive effects. For example, the ACSM reported that regular endurance exercise for 30-60 min on three days of the week in high-normal and Stage 1 hypertension may cause systolic and diastolic pressure drops by 7.4 and 5.8 mmHg, respectively. These decreases in BP seem small, but small decrements in systolic and diastolic pressures of 2 mmHg reduce the risk of stroke by 14% and 17% and the risk of coronary artery disease by 9% and 6%, respectively. In high-normal and Stage 1 hypertension, exercise may be a better therapeutic strategy compared with medications because the expense and potential side effects from chronic medications are reduced. Moreover, aerobic exercise decreases other risks of heart and blood vessel disease, lowers body fat and improves insulin resistance, glucose intolerance and dyslipidaemia. In this regard, aerobic exercise is also recommended for improving and preventing metabolic syndrome.

The anti-hypertensive effect induced by aerobic exercise is not limited to humans. Spontaneously hypertensive rats (SHR) have been used to investigate the effects of exercise on the progression of hypertension, revealing that aerobic exercise lowers their BP. Schluter et al. recently summarised the exercise-induced effects on BP in young (pre-hypertensive) and mature (established hypertension) SHR by performing a meta-analysis of animal studies undertaken from 2002 to 2008, revealing that a significant fall (approximately 15 mmHg) in BP was observed in SHR that started an exercise programme in the prehypertensive or very early hypertensive stage (i.e. 4–6 weeks). Either treadmill running (low-to-moderate intensity, 5 days/week for 2–3 months) or free-wheel running inhibited BP progression in SHR. Evenwel and Struyker-Boudier also reported a decrease in BP (approximately 25 mmHg) with forced swimming (1 h/day, 5 days/week for 2 months) in SHR who started an exercise programme in the pre-hypertensive or very early hypertensive stages (4–5 weeks), suggesting that the type of aerobic exercise is not a limiting factor for positive effects on BP. We also found there were significant reductions in BP (approximately 10 mmHg) among 4-week-old SHR after 12 weeks of free-wheel running, demonstrating that exercise has anti-hypertensive effects in at least pre-hypertensive and mild hypertensive humans and rats.

What mechanisms are involved in the anti-hypertensive effects of exercise? BP (mean pressure) is expressed by the product of cardiac output (CO) and systemic vascular resistance. CO is defined as the product of stroke volume (SV) and heart rate (HR). Because aerobic exercise training is usually accompanied by an increase in heart function observed by an elevation of SV, and HR may be either unchanged or slightly decreased, a reduction in CO is unlikely to be the reason for exercise training-induced reductions in BP. Daily aerobic exercise training reduces the total systemic vascular resistance (SVR) in hypertensive patients. As ACSM points out, many factors may contribute to the reduction of vascular resistance. Aerobic exercise training decreases sympathetic outflow, attenuating vascular responses to vasoactive monoamines and peptides such as noradrenalin and endothelin-1. In addition, aerobic exercise increases nitric oxide (NO) production and capillary remodelling in skeletal muscles; all of which can decrease peripheral vascular resistance. Thus, the mechanisms underlying the anti-hypertensive effects of exercise involve many factors. Of these, we particularly focused on the effects of exercise on the sympathetic nervous system (SNS) because excessive sympathetic activation is recently considered to be a major factor contributing to EH.

Mechanisms of hypertension—role of the sympathetic nervous system (SNS)

Before discussing the potential mechanisms underlying the anti-hypertensive effects of exercise, it is important to understand the mechanisms of EH. Although they are not fully understood, one common form of EH is neurogenic hypertension, which is maintained by excessive sympathetic activity, and may even be a causative factor because it pre-dates the onset of pathology. Further, some hypertensive animal models such as SHR, Dahl salt-sensitive rats and angiotensin II (ANGII)-induced hypertensive animals have - or are considered to have - increased basal sympathetic nerve activity, which results in hypertension through several factors, including increased peripheral resistance due to vasconstriction.

Sympathetic pre-motor neurons controlling vasomotor sympathetic nerve activity (SNA) are located primarily in the rostral ventrolateral medulla (RVLM). These neurons receive excitatory and inhibitory inputs from other brain areas, such as the hypothalamus and other parts of the medulla oblongata. One of the most important neural regulatory mechanisms in cardiovascular homeostasis is the baroreceptor reflex. The nucleus of the solitary tract (NTS) is the primary termination site of the baroreceptor afferents (Fig. 1). Second (or higher)-order NTS neurons excite gamma-aminobutyric acid (GABA)ergic inhibitory neurons in the caudal ventrolateral medulla (CVLM) that inhibit RVLM neurons, thereby decreasing sympathetic pre-ganglionic outflow (Fig. 1). Given that the baroreceptor reflex function is attenuated in neurogenic hypertension, the abnormal functions in the central arc of the reflex may contribute to neurogenic hypertension. In fact, we previously found that microinjection of CoCl2, a non-selective neurotransmission blocker, into NTS dramatically increased BP in normotensive rats (Wistar Kyoto: WKY rats) and SHR; however, the response was more highly attenuated in the latter than in the former (H. Waki et al, unpublished data). Thus, attenuation of NTS functions may contribute in part to neurogenic
hypertension in SHR (Fig. 1). Moreover, the altered NTS functions in SHR may be due to increased GABAergic responses within the NTS.21 The mechanisms underlying altered GABAergic functions in the NTS are likely to be triggered by several factors; one of these may be an abnormal inflammatory condition in NTS. Indeed, some inflammatory molecules such as junctional adhesion molecule (JAM)-A, leukotriene B4 (LTB4) and chemokine (C-C motif) ligand 5 (Ccl5), and their related genes such as JAM-A, LTB4 12-hydroxydehydrogenase (12-HD), Ccl5, CC chemokine receptor 1 (Ccr1), Ccr3, chemokine binding protein 2 (Ccbp2) and tumor necrosis factor (ligand) superfamily member 4 (Tnfsf4) were all abnormally expressed in the NTS of hypertensive animals.22-24 These profiles were also identified to functionally contribute to hypertension phenotypes by modulating NTS neurons.22-24

The hypothalamic paraventricular nucleus (PVN) is another brain area that controls BP by modulating the RVLM neurons. PVN receives excitatory inputs from the organum vasculosum of the lamina terminalis (OVLT) and the subfornical organ (SFO), which lie outside the blood–brain barrier and can detect plasma osmolarity and ANGII in the blood. In salt-sensitive and ANGII-induced hypertension, excitation of these pathways can result in neurogenic hypertension. Altogether, many areas of the brain are likely to be involved in the mechanisms underlying neurogenic hypertension, which complicates our understanding of these detailed mechanisms of EH.

**Exercise training and the sympathetic nervous system**

As mentioned above, changes in sympathetic nervous system activity is considered to be an underlying mechanism for the anti-hypertensive effects of exercise. For

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**Fig. 1** Nucleus of the solitary tract (NTS) may be a key cardiovascular centre for the anti-hypertensive effects of exercise training. The brainstem cardiovascular centers, which regulate sympathetic output, include the NTS, caudal ventrolateral medulla (CVLM) and rostral ventrolateral medulla (RVLM). NTS reportedly exerts an important role in regulating cardiovascular responses during exercise. It is the central termination site for baroreceptor input and also receives numerous inputs from other brain areas, including the dorsomedial hypothalamus (DMH) or hypothalamic paraventricular nucleus (PVN) (i.e. the candidate pathways of the central command) (A). NTS also receives direct projections from spinal dorsal horn neurons, which transmit afferent inputs from skeletal muscle (B). Therefore, NTS is considered to be a central site that integrates the descending and ascending inputs while regulating baroreceptor function during exercise. This suggests NTS is likely to be one of the cardiovascular centres where functional and neuroanatomical plasticity occurs by exercise training. Moreover, based on our previous reports, attenuation of NTS functions contributes in part to neurogenic hypertension (C, see text). Taken together, exercise training appears to alter NTS functions, which may contribute to a decrease in the basal level of sympathetic activity in mild hypertensive humans and rats. TMN: tuberomammillary nucleus, NA: nucleus ambiguus, IML: intermediolateral cell column.
example, reductions in plasma norepinephrine have been reported after endurance training in mild EH, which may be due to decreased spillover rather than increased clearance, suggesting a decrease in sympathetic activity. Moreover, training-induced decreases in BP in older mild-hypertensive subjects were associated with reduced norepinephrine release. Laterza et al. recently demonstrated this phenomenon by directly measuring sympathetic activity in muscles (i.e., microneurography) in Stage 1 hypertensive patients. Subjects cycled on an ergometer bicycle for 40 min 3 days/week for 4 months, after which the effects of exercise were compared between hypertensive and normotensive subjects. They found that the resting level of sympathetic activity decreased in hypertensive patients, but this effect was not observed in hypertensive patients who did not exercise or in exercising normotensive subjects. BP levels also decreased only in hypertensive subjects, suggesting that higher basal sympathetic activity and BP are important factors for the expected results of exercise. Because the level of sympathetic activity is regulated by the baroreceptor reflex, understanding the effect of exercise training on the reflex system in hypertensive patients is important. Laterza et al. found that baroreceptor-dependent sympathoinhibition induced by phenylephrine infusion was lower in hypertensive patients than normotensive patients. However, the reflex response in hypertensive patients after an exercise training period increased to the same level as that of normotensive patients. Again, these exercise-induced effects were not observed in subjects with hypertension who did not exercise or in exercising normotensive subjects. These findings demonstrate that a decrease in basal sympathetic activity through exercise training in patients with hypertension may be mediated, at least in part, by an improved baroreceptor reflex.

Moraes-Silva et al. demonstrated the significance of plasticity in the baroreceptor reflex with exercise training in an animal model of hypertension in which SHR (2-months old) exercised on a treadmill (50–70% of the maximum speed for 1 h, 5 days/week for 10 weeks). They found that the baroreceptor cardiac reflex was lower in SHR than in normotensive control rats; but in SHR, exercise training improved the reflex functioning to levels similar to those of normotensive rats. Similarly, the index of vasomotor sympathetic outflow (low frequency power in systolic pressure variability) and BP decreased significantly in SHR with exercise training. Their data also suggest that even established hypertension (approximately 195 mmHg systolic pressure) in SHR can be treated with a carefully monitored treadmill exercise programme from an early age (2 months old). Most importantly, they found that with sinoaortic denervated SHR (i.e. the baroreceptor reflex was not functional), the same exercise protocol did not affect cardiovascular activity in the same manner, suggesting that the baroreceptor reflex is essential for the anti-hypertensive effects of exercise.

Taken together, exercise training in both EH and hypertensive animals appears to increase the baroreceptor reflex function, which may contribute to a decrease in the basal level of sympathetic activity.

**Why can exercise training be expected to affect resting BP levels?**

To evaluate the effect of exercise training on BP in hypertensive patients, the basal level (i.e., resting BP) is measured and compared before and after exercise training. How does exercise training affect basal BP and sympathetic activity? The physiological adaptation resulting from exercise training is likely to occur to improve exercise performance. The basal levels of physiological parameters observed after an exercise training period is likely to be secondary to the cardiovascular adaptive responses during exercise. In this regard, the regulatory mechanisms of the sympathetic nervous system that are active during exercise should be further examined.

Generally, a single bout of exercise induces a moderate increase in BP with marked tachycardia resulting from sympathoexcitation, which induces vasoconstriction in the major organs (but not in skeletal muscles) and activates heart function. The neural mechanisms underlying cardiovascular regulation during exercise are discussed in our recent review. In short, with a single bout of exercise, neural signals from the central command are directly or indirectly projected to the NTS and RVLM (Fig. 1). The signals sent to the RVLM activate sympathetic pre-motor neurons that, in turn, induce a pressor response and tachycardia. The signals sent simultaneously to the NTS reset the functional range of the baroreceptor reflex to a higher pressure level by modulating the NTS neurons. The GABAergic interneurons in the NTS may be involved in resetting the baroreceptor reflex by limiting the extent of excitation of barosensitive NTS neurons, and therefore can continuously increase sympathetic activity during exercise. However, it should be noted that the baroreceptor reflex remains functional to avoid further increases in sympathetic activity during exercise. In other words, the reflex system is crucial for cardiovascular homeostasis during exercise. This was observed in our previous study that demonstrated a pressor response during a single bout of exercise in sino-aortic denervated rats (i.e., the baroreceptor reflex was not functional) to be larger than that of control animals (Fig. 2). Taken together, a single bout of exercise may trigger the central pathways involved in both pressor responses (i.e., central forward and muscle feedback mechanisms) and cardiovascular homeostatic responses (i.e., the baroreceptor reflex) (Fig. 3). Moreover, exercise training induces plasticity in both central pathways that regulate the cardiovascular system during exercise (Fig. 3). Adaptive changes in the central
mechanisms for pressor responses (i.e. the central command or feedback mechanism) may be essential for cardiovascular regulation during exercise and may contribute to increased exercise performance9). On the other hand, considering the nature of the baroreceptor reflex function for BP homeostasis, we postulate that adaptive facilitation in reflex functioning may play an important role in controlling sympathetic activity, even at rest; and this may prevent an increase in basal BP in pre-hypertension and reduce high resting BP levels in mild hypertension (Fig. 3).

Thus, exercise training induces anti-hypertensive effects in both pre-hypertension and mild hypertension.

We then examined how the baroreceptor reflex can be facilitated by exercise training. We assumed that repeated electrical stimulation to the brain cardiovascular centres during routine exercise is a main trigger to induce plasticity; although, to our knowledge, only a few studies have investigated the neural mechanisms underlying the anti-hypertensive effects of exercise training. Here, we introduce recent hypotheses on such neural mechanisms primarily on the basis of our recent findings.

Fig. 2  Pressor response during a single bout of exercise in sino-aortic denervated rats.
Exercise-induced pressor response is larger in sino-aortic denervated (SAD) rats (i.e. the baroreceptor reflex was not functional) than that in the control (intact) animals, suggesting that the baroreceptor reflex is crucial to avoid further increases in BP during exercise. Adapted, with permission, from Waki et al. 200332) SBP: systolic blood pressure.

Fig. 3  Schematic illustrations explaining how exercise training affects basal BP (resting BP).
A single bout of exercise may trigger the central pathways involved in both pressor responses (i.e. central command and muscle feedback mechanisms) and cardiovascular homeostatic responses (i.e. the baroreceptor reflex) (left illustration). Exercise training may induce plasticity in these pathways (right illustration). Adaptive changes in the central mechanisms for presser responses may be essential for cardiovascular regulation during exercise and may contribute to increased exercise performance (right, top illustration). On the other hand, adaptive facilitation in reflex functioning may play an important role in controlling sympathetic activity, even at rest (right, bottom illustration), and this may prevent an increase in basal BP in pre-hypertension and reduce high resting BP levels in mild hypertension.
NTS as a key cardiovascular centre for the anti-hypertensive effects of exercise training

As discussed above, the NTS is the central termination site for baroreceptor input and also receives direct projections from spinal dorsal horn neurons, which transmit afferent inputs from skeletal muscle. The NTS also receives numerous inputs from other brain areas, including the dorsomedial hypothalamus or hypothalamic paraventricular nucleus (i.e. the candidate pathways of the central command) (Fig. 1). Therefore, it is considered to be a central site that integrates the descending and ascending inputs while regulating baroreceptor function during exercise. This suggests the NTS is likely to be one of the cardiovascular centres where functional and neuroanatomical plasticity occurs. Moreover, based on our previous reports that abnormal expression of some genes in the NTS are associated with neurogenic hypertension in SHR and EH (Fig. 1) and that angiotensinogen mRNA expression was decreased in the NTS of SHR after treadmill exercise training, whereas we failed to see a reduction in gene expression after a free-wheel running exercise. Therefore, the type of exercise may differentially affect gene expression profiles in the NTS; and, thus, the mechanisms of anti-hypertensive effects may differ among various types of exercise.

Exercise training can induce functional plasticity in the NTS of normotensive animals. This includes neurotransmission properties essential for regulating BP during exercise. Mueller & Hasser reported that increased responsiveness in BP and sympathetic activity induced through NTS inhibition by the GABA_α agonist muscimol were blunted in normotensive rats by treadmill running for 8–10 weeks. This would be an interesting notion if it occurred in SHR considering that the inhibitory effects of exercise training on GABA_α transmission would improve the hypertension phenotype in SHR. De Souza et al. also demonstrated a marked increase in the sensitivity of vasopressin V1 receptors to an endogenous ligand in the NTS following exercise training in normotensive rats. They also found that exercise training enhanced the intrinsic excitability of NTS neurons that receive inputs from PVN. However, this functional plasticity in the NTS may be more important in regulating cardiovascular parameters during exercise than in regulating resting BP levels. Nevertheless, it is interesting to consider whether these observations are also true in the NTS of SHR after exercise training. Our findings obtained in a microarray study so far suggest that exercise training does not alter the gene expression profiles of GABA_α and V1 receptors in the NTS of SHR. Further investigation is required to determine whether exercise training can alter protein expression levels of these molecules. Clearly, whether a similar scenario applies to different types of aerobic exercises such as treadmill running and swimming is uncertain; moreover, different exercise intensities or periods should also be investigated.

On the other hand, our data from the microarray study has provided new insights into the brain mechanisms underlying the anti-hypertensive effects of exercise (Fig. 4). In SHR, exercise training altered the expression levels of NTS genes that are functionally associated with neuroac- tive ligand–receptor interactions. One of those genes was the serotonin 1A receptor (5-hydroxytryptamine, 5-HT; 5-HT_1A) gene. Its physiological agonist, serotonin, regulates the cardiovascular system. We confirmed that serotonin microinjected into the NTS decreases BP and HR as previously reported, but no differences in the cardiovascular response were found between the exercise-trained SHR and the control group. Because the depressor and bradycardia responses are mediated mainly by the 5-HT2A receptor, and the gene expression for this receptor was not affected by exercise training in SHR, such results can be expected. The 5-HT2A receptor is a Gq/G11-protein coupled receptor that induces excitatory neurotransmission and may be expressed in barosensi-
Conclusions

Although the benefit of exercise on hypertension is well recognised, the mechanisms underlying such exercise-induced anti-hypertensive effects remain unclear. In particular, information regarding the neural mechanisms is extremely limited. Here, we proposed that brain plasticity participates in cardiovascular adaptation as described above. Our findings so far suggest that exercise training may not improve causative genetic factors for an animal model of hypertension; however, it alters neuroactive ligand–receptor interactions within the NTS, which regulate basal BP levels. One of these may be a serotoninergic system that may be facilitated by daily exercise training, and may decrease the basal sympathetic output and basal BP level. However, further investigations are required to test this hypothesis and identify whether a similar scenario applies to other areas of the brain that regulate BP, including the hypothalamus and RVLM.
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