Activity-Dependent Plasticity in Central Homeostatic Systems

EXERCISE TRAINING AND SYMPATHETIC NERVOUS SYSTEM ACTIVITY: EVIDENCE FOR PHYSICAL ACTIVITY DEPENDENT NEURAL PLASTICITY

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SUMMARY

1. It has been generally accepted that regular physical activity is associated with beneficial effects on the cardiovascular system. In fact, the idea that exercise maintains cardiovascular health is evident by the direct links between a sedentary lifestyle and the risk of cardiovascular and other disease states.

2. Cardiovascular diseases, such as hypertension and heart failure, are often associated with sympathetic nervous system (SNS) overactivity. Conversely, exercise has been shown to reduce hypertension and decrease elevated SNS activity. In addition, there is evidence that exercise may reduce resting blood pressure and sympathetic outflow in normal individuals.

3. Although somewhat controversial in humans, evidence from animal studies also indicates that exercise training reduces baroreflex-mediated and other forms of sympathoexcitation in normal individuals. Collectively, these data are consistent with the hypothesis that physical activity may decrease, and physical inactivity may increase, the incidence of cardiovascular disease via alterations in SNS activity. Despite the important clinical implications of this possibility, the mechanisms by which exercise alters control of SNS activity remain to be fully elucidated.

4. Recent evidence suggests that central nervous system (CNS) plasticity occurs under a variety of conditions, including varying levels of physical activity. The purpose of the present brief review is to provide evidence that changes within the CNS contribute importantly to altered regulation of the SNS observed following exercise training. The primary hypothesis is that physical activity versus inactivity produces plasticity within neural networks that regulate SNS activity. This hypothesis is supported by published and preliminary data that suggest that exercise training may reduce sympathoexcitation by reducing activation of neurons within cardiovascular regions of the brain. These mechanisms are likely to be important in disease states of sympathetic overactivity and in normal healthy individuals whose risk of cardiovascular disease is reduced by leading an active versus sedentary lifestyle.

Key words: cardiovascular disease, exercise, physical inactivity, sympathetic nervous system.

CARDIOVASCULAR DISEASE, PHYSICAL ACTIVITY/INACTIVITY AND SYMPATHETIC NERVOUS SYSTEM ACTIVITY

Despite significant advances in treatment strategies, cardiovascular disease remains the leading cause of death in the US.1 Among other risk factors, physical inactivity is considered one of the leading causes of cardiovascular disease.2,3 In fact, the combination of a sedentary lifestyle and poor diet has been predicted by the Centers for Disease Control to overtake tobacco as the leading contributor to premature death.2 Therefore, an understanding of the mechanisms by which physical activity and inactivity influence the cardiovascular system is highly relevant from a clinical, economic and public health perspective.

Cardiovascular diseases, such as hypertension and heart failure, are often associated with overactivity of the sympathetic nervous system (SNS).4,5 It has been suggested that increases in physical activity produce beneficial effects on the cardiovascular system in normal and diseased individuals via alterations in neural control of the circulation.6-8 These effects include reductions in blood pressure and sympathetic outflow in humans,6,7,9,10 as well as in animal models of exercise training.6,7,9-18 Because morbidity and mortality in cardiovascular disease are often associated with elevations in SNS activity,19,20 the beneficial effects of physical activity are likely related, in part, to reductions in sympathetic activity.5,13 Understanding the mechanisms by which exercise training alters control of the SNS in health and disease is important for developing new strategies in the prevention and treatment of cardiovascular disease. In addition, a further understanding of these mechanisms may help promote public policy changes that aid in the reversal of the current trends in physical inactivity.
EFFECTS OF PHYSICAL ACTIVITY (EXERCISE TRAINING) ON SNS ACTIVITY

Human studies

One of the difficulties in establishing a conclusive effect of physical activity on SNS activity in humans is likely due to the variety of studies that have attempted to address this seemingly straightforward question. As reviewed by Ray and Hume,21 and examined more recently in a meta-analysis by Cornelissen and Fagard,6 it is clear that individual studies report a variety of effects of exercise training on measures of SNS activity. Exercise training may also influence increases in SNS activity during exercise and in response to other stressors that cause sympathoexcitation, including baroreceptor unloading.21 Furthermore, the type of measurement used to assess SNS activity may influence conclusions on the effects of physical activity in SNS regulation. For example, most studies have used one or more of three basic techniques to assess resting SNS activity: plasma noradrenaline (NA) levels, regional NA spillover or direct microneurographic recordings from nerves innervating skeletal muscle (i.e. muscle sympathetic nerve activity; MSNA). Ray and Hume21 concluded that training has no effect on resting MSNA, whereas Cornelissen and Fagard6 suggest that training reduces plasma NA levels by up to 40%. These data suggest that training may alter NA kinetics or that there may be regionally specific effects of training on SNS activity. The latter hypothesis is supported by at least one study in which training elicited a reduction in renal NA spillover with no change in cardiac NA spillover.10

The significant effects of exercise training on SNS activity may also be influenced by additional factors. These include intersubject variability (for examples, see Jennings et al.22 and Grassi et al.23), age and gender,24 previous and attained fitness levels21,25 and different degrees of adiposity in trained and sedentary subjects.26 Finally, other factors, including the type of training programme, the duration, intensity and frequency of individual bouts and the overall duration of the training programme are all likely to be important factors that warrant further investigation.6,21

Animal studies

In contrast with somewhat equivocal results in humans, evidence from animal studies suggests that increases in physical activity produce consistent reductions in resting and reflex control of sympathetic outflow in normal animals.19 For example, studies of exercise training in rats15,27 and rabbits28,29 indicate a suppression of resting and baroreflex-mediated increases in renal sympathetic nerve activity (RSNA). In addition to a reduction in RSNA, previous studies have also reported blunted baroreflex activation of lumbar sympathetic nerve activity in spontaneous wheel-running rats.30 Finally, there is indirect evidence that treadmill training in rats16,31 and mice17 reduces cardiac sympathetic nerve activity. Therefore, data from well-controlled animal studies appear to indicate a more global effect of exercise training on SNS activity.

EFFECT OF PHYSICAL ACTIVITY VERSUS PHYSICAL INACTIVITY

Perhaps a subtle but important viewpoint that deserves mentioning is that most studies have had the perspective of examining the effects of ‘exercise training’ on cardiovascular variables. This is completely logical because epidemiological studies suggest that physical fitness is beneficial to cardiovascular health.32,33 That said, it is becoming increasingly apparent that a sedentary lifestyle contributes significantly to chronic disease.34 Therefore, if one identifies the trained group as the control or ‘healthy’ group, as has been suggested previously,2 importantly different and significant conclusions can be reached.3 For example, the above-mentioned animal studies suggest that exercise training blunts baroreflex-mediated sympathoexcitation. However, if the trained group is considered the control group, then one could then conclude that sympathoexcitation is actually exacerbated by sedentary conditions. Given the relationship between excess SNS activity and cardiovascular disease and mortality,19,20 it is easy to see how a sedentary lifestyle may be a risk factor for cardiovascular disease due, at least in part, to alterations in SNS activity. That is, physical activity dependent alterations in sympathetic control of the cardiovascular system occurring in otherwise normal ‘healthy’ individuals may be important in reducing the incidence of cardiovascular disease.

ACTIVITY DEPENDENT PLASTICITY IN THE CENTRAL NERVOUS SYSTEM

Increasing scientific evidence is emerging that supports the existence of physical activity dependent plasticity in the central nervous system (CNS). Of particular interest are functional improvements, such as those reported for memory and cognition,35–39 that are associated with changes in the number, structure and function of neurons.35,40 Recent studies indicate that physical activity produces these changes by altering genes involved in synaptic plasticity.41–43 These improvements are associated with factors that are produced within the brain or outside the brain, including, among others, brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF)-I.41,44 Although these studies provide strong support that physical activity beneficially alters cognitive function through alterations in plasticity related genes, it is not known whether exercise produces similar changes in gene expression in regions of the brain that control SNS activity. Evidence discussed below supports the possibility that neurons involved in the control of the SNS also undergo neural plasticity following periods of activity or inactivity.

‘PHYSICAL’ ACTIVITY DEPENDENT PLASTICITY IN NEURAL CONTROL OF THE CIRCULATION

Many studies have now suggested that alterations within the CNS are important in the effects of physical (in)activity on SNS function under both normal and diseased states.8,17,45–52 For example, in spontaneously hypertensive rats (SHR), exercise training reduces the elevated firing rate of caudal hypothalamic neurons.3 These changes are associated with blood pressure reductions and a restoration of GABAergic transmission in this brain region of the SHR.7,32 Exercise training also affects measures of nitric oxide synthase (NOS) activity in the paraventricular nucleus (PVN) of SHR30 and in rats with heart failure.4,51 Changes in NOS within the PVN have been suggested to contribute to training-induced reductions in sympathetic outflow in heart failure animals.3,51 It is important to note that the specific examples mentioned above pertain to the effects of exercise training in animal models of cardiovascular disease and, thus, have important clinical relevance in the treatment of cardiovascular disease with
We hypothesized that the NTS may be overactive in pressure and sympathetic outflow produced by inhibition of the via arterial baroreceptors), as evidenced by large increases in arterial.

The NTS provide a tonic inhibitory influence on SNS activity (primarily mediated sympathoexcitation by recording direct efferent outflow first to demonstrate directly that exercise training blunted baroreflex-mediated sympathoexcitation. Thus, along with others, DiCarlo et al. suggested that centrally mediated alterations were important in the reflex control of the SNS following exercise training. More recent studies have supported these hypotheses by demonstrating changes in neuronal structure and intrinsic firing properties of neurons from physically active versus sedentary animals.

As suggested, these studies can be viewed as beneficial changes induced by exercise training in normal subjects or, conversely, as deleterious alterations induced in individuals that remain sedentary. The remainder of the present review will focus on physical (in)activity induced alterations in the CNS control of SNS activity. Our general hypothesis is that exercise training (vs sedentary conditions) results in differential alterations in the primary central pathways by which SNS activity is regulated. We speculate that these changes ultimately influence cardiovascular health and well-being due to the direct and indirect influences of the SNS on the cardiovascular system and other organ systems that impact the incidence of cardiovascular disease.

**REVIEW OF RECENT WORK**

Owing to the consistent effects of physical activity on baroreflex control of SNS activity in animals, our initial experiments started by examining the basic reflex pathways by which SNS activity is regulated within the brain stem (Fig. 1). Cardiovascular afferents, including those from arterial and cardiopulmonary baroreceptors, terminate at the level of the nucleus tractus solitarius (NTS). The NTS is an important brain region involved in both resting and reflex control of arterial pressure and SNS activity. Neurons within the NTS provide a tonic inhibitory influence on SNS activity (primarily via arterial baroreceptors), as evidenced by large increases in arterial pressure and sympathetic outflow produced by inhibition of the NTS. We hypothesized that the NTS may be overactive in exercise-trained animals and, thus, contribute to reduced sympathoexcitation in the trained state. To test this hypothesis, we inhibited the NTS with bilateral microinjections of the neuroinhibitory compound muscimol in groups of treadmill-trained and sedentary animals. We expected that if the NTS was overactive in exercise-trained rats, it would contribute to greater sympathoinhibition under basal conditions. Therefore, inhibition of neurons in the NTS with muscimol would produce a greater sympathoexcitatory response in trained animals. However, as shown in Fig. 2, we observed blunted pressor and sympathoexcitatory responses to NTS inhibition in trained animals. These data are similar to the blunted baroreflex-mediated sympathoexcitation in most animal models of exercise training and suggested to us that the NTS was not required for expression of blunted sympathoexcitation following exercise training. In addition, a lack of a role for exercise training-induced changes on sympathetic control at the level of the NTS was also supported by additional experiments in which the NTS was activated by glutamate microinjections. Under these conditions, sympathoinhibitory responses to generalized activation of the NTS were not altered by treadmill training. Collectively, these data suggested that alterations downstream from the NTS were responsible for blunted sympathoexcitation observed after exercise training. Our subsequent studies have focused on alterations that may occur at the level of the rostral ventrolateral medulla (RVLM), a brain region critical in the generation of SNS activity.

Rostral ventrolateral medulla neurons project directly to sympathetic preganglionic neurons and inhibition of the RVLM produces blood pressures similar to those observed after complete transection of the spinal cord. These ‘presympathetic’ RVLM neurons are...
believed to be inhibited tonically by GABA, predominantly via GABAA receptors. As demonstrated in Fig. 1, this GABAergic inhibition is generally thought to be mediated by both arterial baroreceptor-dependent and -independent mechanisms.\(^72,74\) We hypothesized that during baroreceptor unloading a greater remaining level of GABAergic inhibition of RVLM neurons could be responsible for blunted baroreflex-mediated sympathoexcitation in trained animals. If so, we would predict that sympathoexcitatory responses to blockade of GABAA receptors in the RVLM of exercise-trained rats would be enhanced. However, as shown in Fig. 3a, bilateral blockade of GABAA receptors with bicuculline resulted in attenuated sympathoexcitatory responses in trained rats.\(^59\) These data suggest that exercise training reduces the sympathoexcitation that occurs via withdrawal of GABAergic transmission, whether it was produced by baroreceptor unloading\(^15,28–30\) or by blockade of GABAA receptors in the RVLM.\(^59\) These data also suggest that GABAAergic inhibition of the RVLM was not augmented by exercise training; otherwise, we would have expected to see a greater response to GABA blockade in trained animals. Therefore, we hypothesized that perhaps a reduced activation of RVLM neurons was occurring and was responsible for diminished sympathoexcitatory responses.

To test whether responses to generalized excitation of the RVLM were reduced by training, we activated the RVLM with microinjections of glutamate (1, 3 and 10 mmol/L) in sedentary and treadmill-trained rats.\(^59\) Consistent with our hypothesis of blunted excitation, glutamate produced sympathoexcitation that was significantly attenuated in exercise-trained compared with sedentary rats (Fig. 3b). A reduced responsiveness of the RVLM to excitatory amino acids following exercise training is supported by a recent report demonstrating reduced pressor responses to glutamate in the RVLM of swim-trained rats.\(^56\) Collectively, these data are consistent with the concept that, following various forms of exercise training in rats, the RVLM is less sensitive to generalized activation with excitatory amino acids.

Because we assessed sympathoexcitatory output from the RVLM by recording lumbar sympathetic nerve activity, it is possible that blunted sympathoexcitation observed in exercise-trained rats could be occurring at the level of the spinal cord, the sympathetic ganglia or both. To address this question, we used Fos immunohistochemistry to examine activation of RVLM neurons in conscious sedentary and treadmill-trained rats. Fos is the protein product of the immediate early gene \(c-fos\) and is produced in response to neuronal activation.\(^75,76\) Fos expression has been used as a marker to identify neural pathways involved in control of SNS activity.\(^77\) In preliminary studies,\(^78\) we produced similar levels of hypotension (< 70 mmHg) in conscious sedentary and trained rats in order to unload arterial baroreceptors of the RVLM with unilateral microinjections of glutamate (30 nL, 10 mmol/L or 300 pmol). Glutamate produced increases in LSNA in Sed rats (\(n = 8\)) that were significantly attenuated in ExTr rats (\(n = 6\)). *\(P < 0.05\) compared with Sed rats. Data modified from Mueller et al.\(^59\)
and activate neurons within the RVLM, similar to previous studies.70–71 Figure 4 demonstrates the number of Fos-positive neurons in the RVLM of sedentary and trained rats under control and hypotensive conditions. Hypotension produced an increase in the number of Fos-positive neurons in the RVLM of both groups compared with control conditions. However, the number of hypotension-induced Fos-positive cells was significantly attenuated in exercise-trained animals compared with sedentary animals. These data suggest that the RVLM was less activated in trained animals despite similar hypotensive stimuli. The afferent input to the brain was also likely similar in both groups because previous studies have reported no change in baroreceptor afferent sensitivity in rats that trained spontaneously on running wheels.57 These data further support our hypothesis that the afferent input to the brain was also likely similar in both groups because previous studies have reported no change in baroreceptor afferent sensitivity in rats that trained spontaneously on running wheels.

![Fig. 4 Fos in the rostral ventrolateral medulla (RVLM), showing the number of Fos-positive nuclei in the RVLM under (a) control conditions or (b) in response to hypotensive conditions in conscious sedentary (Sed; n = 3) rats and exercise-trained (ExTr; n = 4) rats. The ExTr rats exhibited significantly fewer Fos-positive neurons under control conditions and in response to hypotension (†P < 0.05 effect of training; *P < 0.05 effect of hypotension)](image)

To further explore the possibility that increases in physical activity may produce a generalized reduction in sympathoexcitation, we have started to examine differences in the responsiveness of trained and sedentary animals to other stimuli that produce sympathoexcitation. Although muscle contraction has been used as a means to activate RVLM neurons,87 we wanted to circumvent potential changes in SNS activity following periods of physical activity versus inactivity.

Exercise-trained rats also had significantly less Fos-positive nuclei in the RVLM under control conditions compared with sedentary animals (Fig. 4). Although differences in Fos expression under resting conditions are somewhat controversial, these data could suggest that activation of neurons in the RVLM under resting conditions may also be reduced by exercise training. A similar but opposite argument has been made for increases in baseline SNS activity in various models of hypertension, where increased Fos in the RVLM appears to be indicative of sympathetic overactivity in animal models of hypertension.82 If Fos expression in the RVLM under resting conditions is a reflection of baseline sympathetic nerve activity, the present results in trained rats would be consistent with previous studies in humans and animals that have concluded that exercise training reduces resting sympathetic outflow.5,10,15,27

**CROSS-STRESSOR ADAPTATION HYPOTHESIS**

In addition to the mechanisms by which physical activity influences the SNS, we are also interested in the conditions and the extent to which physical activity affects sympathoexcitation. In particular, from data already presented, it is fairly well established that increases in physical activity reduce sympathoexcitation in response to baroreceptor unloading in most animals15,28–30 and some human26 studies. Increases in physical activity could produce a beneficial, chronic reduction in SNS activity simply by reducing the amount of sympathoexcitation that occurs in response to conditions that produce baroreceptor unloading. Alternatively, exercise may produce a generalized reduction in the response to a variety of stimuli and blunted baroreflex-mediated sympathoexcitation is merely an example of this generalized reduction. This hypothesis is by no means novel and has been termed previously, in a broader context, as the Cross-Stressor Adaptation Hypothesis.83 The theory suggests that exercise training, as a stressor on the body, may alter responsiveness to other types of stressors.83 There is support for this theory with specific regard to SNS-mediated responses. For example, pressor responses to different forms of stress are blunted in trained humans21,84 and animals.85,86 In addition, reduced activation of the RVLM has also been shown in response to stress in rats that exercised spontaneously on running wheels.57 Finally, the data presented from our laboratory and others suggest that training reduces cardiovascular responses to generalized activation of the RVLM with microinjections of excitatory agents.58,59,82

For the purposes of our study, this reflex was particularly applicable because it has been shown to not only activate neurons within the RVLM,82 but also require the RVLM for full expression of the cardiovascular response.98,99 Furthermore, this reflex uses excitatory amino acid receptors (i.e. glutamate) at the level of the RVLM to produce increases in arterial pressure.89 Because our treadmill-trained rats have blunted sympathoexcitatory responses to glutamate microinjections in the RVLM (Fig. 3b), we hypothesized that activation of the somatosympathetic reflex would produce blunted sympathoexcitation in trained animals. We tested this hypothesis by stimulation of the central cut end of the sciatic nerve similar to that performed previously.86–89 Our preliminary results,91 shown in Fig. 5a, demonstrate that sciatic nerve stimulation produces increases in sympathetic nerve activity and blood pressure in anaesthetized rats. Furthermore, Fig. 5b represents preliminary data91 that indicate that treadmill training blunts sympathoexcitation produced by activation of the somatosympathetic reflex. It is possible that the blunting of
this reflex involves excitatory amino acid mechanisms at the level of the RVLM; however, additional studies are required to test this hypothesis. Nonetheless, our data and the work of others suggest that exercise training appears to reduce sympathoexcitation to a variety of centrally mediated sympathoexcitatory stimuli. If so, a reduction in sympathoexcitation may contribute, in part, to the reduced incidence of cardiovascular disease in physically active individuals. Conversely, sedentary conditions may produce relatively heightened sympathoexcitatory responses that, over time, could contribute to cardiovascular disease.

**CONCLUSIONS**

Sympathetic overactivity is common in many cardiovascular disease states and is related to a higher incidence of morbidity and mortality. Reductions in sympathetic outflow, whether at rest or during conditions that produce sympathoexcitation, may occur following exercise training. Alterations in cardiovascular regions of the brain stem and other regions that are influenced by levels of physical activity are likely to play a role in long-term cardiovascular health. Future studies will be important in further identifying the central mechanisms that are involved in physical activity dependent changes in the control of SNS activity.

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