PHYSICAL (IN)ACTIVITY DEPENDENT ALTERATIONS
AT THE ROSTRAL VENTROLATERAL MEDULLA:
INFLUENCE ON SYMPATHETIC NERVOUS SYSTEM REGULATION

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Abstract

A sedentary lifestyle is a major risk factor for cardiovascular disease, and rates of inactivity and cardiovascular disease are highly prevalent in our society. Cardiovascular disease is often associated with overactivity of the sympathetic nervous system, which has both direct and indirect effects on multiple organ systems. Although it has been known for some time that exercise positively affects the brain in terms of memory and cognition, only recently have changes in how the brain regulates the cardiovascular system been examined in terms of physical activity and inactivity. This brief review will discuss the evidence for physical activity-dependent neuroplasticity related to control of sympathetic outflow. It will focus particularly on recent studies from our laboratory and others which have examined changes that occur in the rostral ventrolateral medulla (RVLM), considered one of the primary brain regions involved in the regulation and generation of sympathetic nervous system activity.
Introduction

Physical inactivity is a major risk factor for cardiovascular disease (106), the leading cause of death in the United States (62; 84). Despite this relationship, rates of physical inactivity are prevalent in our society (107) and recent studies indicate that more people are dying as a result of physical inactivity than any other preventable risk factor (12). Inactivity-related diseases also continue to produce an increasing economic burden on our health care system. Direct costs for cardiovascular disease associated with inactivity have been estimated at over 23 billion dollars per year (110). Similarly, the cost of inactivity-related diseases such as hypertension has been estimated to be over 63 billion dollars (106). In spite of this substantial investment, as many as two thirds of hypertensive patients have poorly controlled blood pressure (18). It is critical then that we continue to further identify the mechanisms by which major cardiovascular risk factors such as physical inactivity contribute to cardiovascular disease. New insights into mechanisms that predispose individuals to cardiovascular disease could lead to new therapeutic strategies designed to combat cardiovascular disease and thereby lessen the burden on the population and our health care system.

Cardiovascular diseases are often characterized by overactivity of the sympathetic nervous system and this is apparent in both humans and laboratory animal models (4; 29; 31; 35; 52; 90; 100; 112). Sympathetic nervous system activity is influenced by multiple sites within the brain (22; 35). Several of these brain regions have been shown to be altered in models of physical activity and inactivity including (but not limited to) the nucleus tractus solitarius, paraventricular nucleus of the hypothalamus, and the rostral ventrolateral medulla (41; 68; 71; 74; 77; 80; 81). These
alterations occur across a variety of animal models in which physically active animals (treadmill or spontaneous running) have been compared to animals under “normal” cage conditions and termed sedentary (68; 74; 80; 81). In addition, animals under “normal” cage conditions have also been compared to hindlimb unloaded rats, a model of spaceflight or bedrest inactivity (41). These alterations can be termed “physical activity-dependent neuroplasticity” and could contribute importantly in the prevention or development of cardiovascular disease in physically active or sedentary individuals, respectively (74). Since the RVLM has been implicated in several disease states associated with sympathetic overactivity, it is highly likely that the RVLM is involved in altered sympathetic regulation in sedentary versus physically active individuals and the associated predisposition toward chronic disease associated with an inactive lifestyle.

Sympathetic overactivity and cardiovascular disease

When sedentary subjects (humans or animals) are compared to physically active “controls”, the sedentary groups may exhibit enhancement in risk factors for cardiovascular disease including increased resting and baroreflex mediated sympathoexcitation (19; 23; 27; 33; 58; 67; 79; 89; 113). Similarly, studies in laboratory animals suggest that remaining sedentary increases vascular reactivity (16; 50; 97), decreases insulin sensitivity (59), increases visceral adiposity (60) and other markers for cardiovascular disease (14). While differences in resting blood pressure and sympathetic nervous system activity are often not observed between sedentary and physically active humans (86; 87; 93; 94; 105), there is strong evidence that inactivity-related diseases such as hypertension, obesity and diabetes are associated with
overactivity of the sympathetic nervous system (29; 35; 52; 90; 100). Furthermore, increasing physical activity under these conditions of sympathetic overactivity, such as heart failure, has been shown to lower resting sympathetic nerve activity in humans (24; 32; 89) and laboratory animals (113). Overactivity of the sympathetic nervous system can produce detrimental effects on both cardiovascular and non-cardiovascular target organs and thus may contribute to a variety of disease states (31). In addition, there is growing evidence that the mechanisms by which physical activity produces beneficial effects (and physical inactivity produces detrimental effects) may extend beyond those associated with more traditional risk factors (51). One possibility involves alterations in central neural networks that regulate sympathetic outflow (51; 74). Collectively, the current evidence suggests that remaining sedentary may increase the propensity for cardiovascular disease via effects on brain regions important in sympathetic nervous system regulation.

Physical (in)activity-dependent neuroplasticity in sympathetic nervous system regulation

Over the past 10 years increasing evidence indicates that physical activity alters neuronal structure and function in brain regions involved in learning and memory (30; 56; 82; 109). This physical activity-dependent neuroplasticity has generally been thought to be restricted to higher brain regions such as the hippocampus (109). However, recent work suggests that physical activity- and inactivity-dependent changes occur in brain regions important in blood pressure regulation (41; 55; 68; 73; 74; 80; 81; 111; 113). A significant amount of the evidence for central nervous system
mechanisms has come from models in which cardiovascular disease is already evident (i.e. hypertension, heart failure, etc) (41; 55; 68; 73; 111; 113). Although these studies are highly clinically relevant and suggest reversal of changes associated with disease states, there is also increasing evidence that in the absence of overt disease, physical activity or inactivity alone can produce central alterations that influence sympathetic nervous system regulation (74; 80; 81). Our recent study comparing spontaneous wheel running to "normal" cage activity emphasized this point and suggested that a sedentary lifestyle alone or in combination with other cardiovascular risk factors may contribute to cardiovascular disease via influences on central structures involved in regulation of the sympathetic nervous system (75). We have focused our efforts on the RVLM as a key brain region involved in the generation of sympathetic outflow.

Role of the rostral ventrolateral medulla in health and disease

The RVLM is considered one of the most important brain regions involved in control of basal and reflex changes in activity of the sympathetic nervous system (20; 21; 35; 38). Under normal conditions, bulbospinal neurons in the RVLM play a key role the integration and generation of central sympathetic drive via projections to sympathetic preganglionic neurons in the intermediolateral cell column of the spinal cord (21; 36; 37). The activity of RVLM neurons is regulated by both excitatory and inhibitory neurotransmitters (21; 38). While a number of neurotransmitters have been localized in the RVLM (85; 102), glutamate and γ-aminobutyric acid (GABA) appear to be the primary excitatory and inhibitory neurotransmitters, respectively. Sympathoexcitatory neurons in the RVLM have been classified into two major groups
based on the presence (C1 neurons) or absence (non-C1 neurons) of
phenylethanolamine-N-methyl transferase (PNMT), the enzyme responsible for the
synthesis of epinephrine (21; 38; 65; 69; 104). All C1 neurons are generally considered
sympathoexcitatory and comprise up to 70% of barosensitive RVLM neurons that
project to the spinal cord (91; 104). Specific lesioning of C1 cells reduces reflex
sympathoexcitation and diminishes responsiveness of the RVLM to microinjections of
glutamate (63; 64; 92). However, generalized inhibition of the RVLM is required to
eliminate a variety of cardiovascular reflexes and decrease blood pressure and
sympathetic nerve activity to levels observed after complete spinal cord transection or
ganglionic blockade (20; 36; 48). These data imply that the RVLM and in particular,
both C1 and non-C1 neurons within the RVLM, are critically important in the
maintenance and activation of sympathetic nervous system activity and control of blood
pressure (20; 21; 38).

A growing body of literature indicates that the RVLM is also involved in
pathophysiological increases in the activity of the sympathetic nervous system (11; 46;
47; 78; 98; 102). For example, elevations in arterial pressure in various models of
hypertension, including obesity related hypertension, are dependent on neuronal activity
in the RVLM (11; 46; 47; 78; 98). The increased output of the RVLM in hypertension is
likely dependent on increased excitatory input from other brain regions as well as an
increase in sensitivity to excitatory input (3; 4; 11; 17; 45; 45; 108). Interestingly, the
increase in sensitivity to excitation may occur together or separately from the increased
tonic excitatory input depending on the model or risk factor studied. For example, in
some (but not all) models of hypertension, augmented sympathoexcitation is attributed
to increased tonic excitatory glutamatergic input to the RVLM (3; 4; 11; 17; 45; 45; 108).
In addition, pressor and sympathoexcitatory responses to direct activation of the RVLM are enhanced in some models (11; 17; 108) but not in others (78; 95; 96; 102; 103).
Interestingly, Dahl-salt resistant rats that remain normotensive after being fed high salt, exhibit enhanced pressor responses to glutamate in the RVLM yet exhibit little or no response to blockade of ionotropic glutamate receptors (47). We have observed similar results when comparing sedentary versus physically active rats (76), suggesting that increased sensitivity to excitation may occur in the absence of an overt change in tonic excitatory input. Furthermore, these data suggest that the influence of the different risk factors (i.e. dietary salt, inactivity, etc.) may occur via similar or disparate mechanisms within the RVLM, and in combination, produce additive or synergistic effects on sympathetic outflow and the development of cardiovascular disease.

Proposed role of the rostral ventrolateral medulla in physical (in) activity dependent changes in SNA regulation

Figure 1 contains a generalized schematic of the wide variety of inputs to the RVLM and its crucial role in the regulation of sympathetic activity and blood pressure. It also demonstrates how this regulation may be affected by exercise or physical inactivity. As the RVLM receives a variety of cardiovascular and exercise-related inputs (20; 21; 38), it is not surprising that it has been shown to be activated during acute bouts of dynamic exercise (49), in response to muscle contraction (7; 9), and stimulation of group III and IV afferents (72; 99). Pressor and sympathoexcitatory responses occurring under these conditions appear to be mediated by release of glutamate acting
on ionotropic receptors in the RVLM (5; 8; 54). Along with feedback from exercising muscle (53), higher brain centers also contribute to the cardiovascular response to acute exercise via direct and indirect projections to brainstem pathways that likely involve the RVLM (25; 26; 28; 42; 57; 83).

Although glutamate and other neurotransmitters in the RVLM appear to be involved in the cardiovascular response to acute exercise (61; 88), the influence of repeated bouts of exercise (i.e. regular physical activity) and the recurring, often cyclical activation of these exercise-related inputs on the RVLM are likely to be important in terms of neuroplastic changes. Conversely, in the absence of these repetitive inputs (i.e. a sedentary lifestyle/ "normal" cage activity), similar or additional mechanisms may contribute to altered regulation of sympathetic outflow and blood pressure observed in sedentary subjects. Recently, our laboratory and others have demonstrated that when compared to physically active animals, sedentary animals (which lack repetitive exercise-related inputs) exhibit enhanced blood pressure (66) and sympathoexcitatory responses (76) to direct glutamatergic activation of the RVLM. These data suggest that alterations occurring at the RVLM may be responsible for enhanced sympathoexcitation in sedentary animals (See #1-4 on Figure 1 under Changes at RVLM). Furthermore, responses to angiotensin II microinjection in the RVLM are not enhanced in sedentary versus physically active animals (10), suggesting that enhanced excitation to glutamate is not due to a generalized effect on neuronal excitability as appears to occur in animals on excess dietary salt (1; 2).

GABA tonically suppresses the activity of RVLM neurons, primarily by activation of GABA_A receptors (6; 13; 43; 70; 101). We hypothesized that enhanced
sympathoexcitation to glutamate microinjections observed in sedentary animals could be due to reduced GABAergic inhibition of RVLM neurons. If GABAergic tone was reduced in the RVLM of sedentary rats then we would have expected that responses to blockade of GABA_A receptors would also be reduced compared to physically active animals. However, we have observed that blockade of GABA_A receptors in the RVLM produced enhanced (not reduced) responses in sedentary rats compared to treadmill exercised rats (76). We interpreted these data to suggest that enhanced sympathoexcitation in sedentary rats was not due to reduced GABAergic inhibition of the RVLM, but that these neurons may receive more excitatory input or be more sensitive to persisting excitatory glutamatergic input following removal of GABAergic tone. In additional experiments, blockade of ionotropic glutamate receptors alone in the RVLM did not reveal differences in tonic glutamatergic excitation of RVLM neurons in sedentary or physically active rats (76). These data indicate that individual RVLM neurons may be more sensitive to excitatory glutamatergic input and/or that more RVLM neurons participate in glutamatergic-mediated sympathoexcitation in sedentary animals (See #1 and 2 on Figure 1). Our observation of enhanced sympathoexcitatory responses to glutamate microinjections in sedentary animals supports either possibility (76), however, previous studies indicate an increased number of activated RVLM neurons (determined by Fos labeling) in sedentary versus physically active animals under various conditions including acute exercise (44) and acute stress (34). These findings suggest that more RVLM neurons may be recruited to produce sympathoexcitation following sedentary versus physically active conditions. In either case, we speculate that the increased sensitivity to glutamate in the absence of a
change in tonic input is due to the lack of repetitive activation of glutamate receptors in the RVLM of sedentary compared to physically active animals. Furthermore, we contend that neuroplasticity in glutamate receptor-mediated neurotransmission in the RVLM may be at least one important target by which physical activity and inactivity influence regulation of sympathetic outflow. It is possible that these alterations occur in the absence of any overt structural plasticity since Nelson and colleagues have reported no alterations in dendritic branching in Golgi-Cox impregnated neurons examined in the region of the RVLM of sedentary versus spontaneously exercising rats (80; 81). Whether enhanced sympathoexcitation observed in sedentary animals is due to increased activation of individual RVLM neurons, increased recruitment of spinally-projecting RVLM neurons, or both is unknown.

**Perspectives and Significance**

One subtle yet important question is whether the relative difference between sedentary and physically active groups is due to the effects of being sedentary, the effects of being physically active, or a combination of both. Figure 2 illustrates this point graphically. The gray area represents the time period from our previous study in which enhanced responses to activation of the RVLM were observed in sedentary versus physically active animals (76). For simplicity, the y-axis is labeled “RVLM responsivity”, and examples A, B, and C represent some of the basic possibilities by which these differences could develop over time. In example A, maintaining sedentary conditions (red, dotted line) may increase RVLM sensitivity while physically active conditions (green, solid line) may attenuate or prevent this increase. In example B, maintaining
sedentary conditions may slightly increase or not affect RVLM sensitivity; whereas, allowing animals to exercise may reduce RVLM sensitivity. Finally, in example C, RVLM sensitivity may decrease over time in animals that are allowed to exercise but to a lesser extent in sedentary animals. Certainly, these possibilities are not mutually exclusive and more complex possibilities may occur. A fundamental contention is that by examining the development of these differences over time, it may be possible to separate out the potential mechanisms by which physical activity versus inactivity contribute to the relative differences observed. In addition, examination of a variety of factors including the type of exercise (aerobic versus resistance); duration; intensity; environmental conditions; and individual responsiveness to exercise or inactivity are important, clinically relevant issues. Like other laboratories (39; 40; 60), we continue to promote the development of experimental designs and models that examine this fundamental question by treating the sedentary condition as a contributing factor to chronic disease, and physically active conditions as the “normal” healthy control (15; 75). We feel that this reflects more than a semantic difference, but rather reflects an important and distinct paradigm shift as to what should be considered a “normal” or “control” group.

The evidence reviewed strongly supports the need to identify the mechanisms by which a sedentary lifestyle contributes to enhanced sympathoexcitation at the level of the RVLM and the impact of these alterations on sympathetic control of blood pressure. Important questions remain including how RVLM neurons individually and as a population process, integrate and produce sympathetic drive. Other brain regions via projections to the RVLM and spinal cord are also likely to play important roles as well.
Understanding these mechanisms is important because of the obvious impact of physical inactivity on the health of the population. In fact, physical inactivity is considered by some as “the biggest health care problem of the 21st century” (12). The knowledge gained from future studies may ultimately allow the development of novel therapeutic strategies for cardiovascular diseases associated with a sedentary lifestyle.
FIGURE LEGENDS

**Figure 1.** Schematic diagram illustrating the role of the rostral ventrolateral medulla (RVLM) in the integration and generation of sympathetic outflow. Potential influences of chronic exercise versus chronic inactivity are presented that could affect sympathetic nerve activity (SNA) and its direct and indirect effects on blood pressure and cardiovascular disease.

**Figure 2.** Hypothetical possibilities to describe the relative differences in the responsiveness of the RVLM in sedentary versus physical active animals. Examples are represented over time and include (A) attenuated increases in active animals over time, (B) increases in sedentary and decreases in active animals over time, or (C) attenuated decreases in sedentary animals over time. The responsiveness of the rostral ventrolateral medulla (RVLM responsivity) is based on results of different studies that suggest the RVLM is activated to a greater extent in sedentary versus physically active animals (34; 44; 66; 76).
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**Input from Higher Centers:**
- Central Command
- Hypothalamus
- Regions Receiving Afferent Input

**Chronic Exercise**

**Brainstem Pathways**

**Exercise-Related Afferent inputs:**
- Baroreceptors
- Metaboreceptors
- Mechanoreceptors

**RVLM**

**Changes at RVLM leading to enhanced SNS outflow:**
1. ↑ sensitivity of neurons
2. ↑ recruitment of neurons
3. ↑ excitatory input
4. ↓ inhibitory input

**Changes Related to Inactivity That Could Lead to Enhanced Sympathoexcitation:**
- Exercise-Related Input
- Adipose Tissue
- Insulin sensitivity
- Renin/Angiotensin System

**Blood Pressure**
- ↓ CV Disease

**SNA**
- ↓

**Blood Pressure**
- ↑ CV Disease
A

RVLM responsivity

Study period

“Sedentary”

Relative Difference

“Active”

B

RVLM responsivity

“Sedentary”

Relative Difference

“Active”

C

RVLM responsivity

“Sedentary”

Relative Difference

“Active”

Time

1 wk

4 wks

8 wks

10 wks