Published in final edited form as:
Exerc Sport Sci Rev. 2010 July ; 38(3): 122–127. doi:10.1097/JES.0b013e3181e372b5.

Postexercise Hypotension: Central Mechanisms

Chao-Yin Chen[1] and **Ann C. Bonham**[1,2]

[1]Department of Pharmacology, University of California, Davis, CA, USA

[2]Department of Internal Medicine, University of California, Davis, CA, USA

Abstract

A single bout of exercise can lead to a postexercise decrease in blood pressure in hypertensive individuals, called postexercise hypotension. Compelling evidence suggests that the central baroreflex pathway plays a crucial role in the development of postexercise hypotension. This review focuses on the exercise-induced changes in brainstem nuclei involved in blood pressure regulation.

Keywords

baroreflex; brainstem; exercise; hypertension; neuroplasticity

INTRODUCTION

Hypertension is a major antecedent of stroke, heart failure, and end-stage renal disease (20). It is estimated that one in three U.S. adults has high blood pressure and about 25% of the U.S. population 20 years or older has prehypertension (20). The estimated direct and indirect cost of high blood pressure for 2009 is $73.4 billion USD (20). Alarmingly, of adults (≥ 20 years of age) with hypertension, only 31% had it under control with pharmacological treatments (20). A single bout of mild to moderate exercise can lead to a postexercise decrease in blood pressure in hypertensive individuals, called postexercise hypotension (PEH). PEH can last for up to 13 hours in humans, and could be an effective non-pharmacological antihypertensive strategy (18). Despite the well-documented blood pressure lowering effect of exercise, the central neuronal mechanisms have only recently been revealed. This review focuses primarily on new evidence of fundamental synaptic mechanisms in the central baroreflex pathway that contribute to development of PEH. Based on work from our laboratory (5,7,17) and other's (28) in exercise and blood pressure regulation, we have derived the idea that an elegant interaction between substance P and the inhibitory synaptic transmission in the brainstem that contributes to PEH.

POSTEXERCISE HYPOTENSION

The observation of post-exercise hypotension can be traced back as early as 1971 (14). In a clinical communication, Groom reported a consistent decrease in systolic and diastolic blood pressure in runners immediately after running at an estimated speed of 6 MPH for over four hours (14). Ten years later, Fitzgerald reported a personal observation that jogging at 70% of

Correspondence: Chao-Yin Chen, Ph.D. University of California, Davis Department of Pharmacology GBSF3510C, One Shields Avenue Davis, CA, USA 95616 Phone:(530) 754-6458 Fax: (530) 752-7710 cych@ucdavis.edu.

maximum oxygen consumption for 25 minutes decreased labile pressure to near normal levels that lasted for several hours, sometimes up to 10 hours (12). Postexercise hypotension has since been confirmed in normo- and hypertensive humans, as well as in animal models of hypertension (18). PEH is more prominent and predictable in hypertensive individuals although it occurs in both normo- and hypertensive individuals (18). In humans, PEH has been documented following various types of exercise, including walking, running, cycling, swimming, and resistance exercise (18,26). In spontaneously hypertensive rats (SHRs), dynamic exercise (running) as well as electrical stimulation of skeletal muscles (isometric contraction) can induce PEH (18). While a short bout of low intensity exercise effectively produces PEH, more prolonged and/or higher intensity exercise results in a greater decrease in blood pressure and longer PEH duration (21,25–26).

PERIPHERAL VERSUS CENTRAL MECHANISMS IN PEH

Several peripheral hemodynamic changes occur after exercise, including changes in regional and total peripheral resistance, cardiac output (stroke volume and/or heart rate), and plasma volume (20). Nevertheless, reports appear to vary from study to study, perhaps due to the complexity of interactive factors involved in each of these measurements (18). There is evidence that mechanisms operating in the central nervous system (CNS) may be important. Gene expression of preproenkephalin increases in the CNS after treadmill exercise in SHRs (3), and the opioid receptor antagonist, naloxone, attenuates PEH in both humans and SHRs (18). Injections of a vasopressin V1 receptor antagonist into the lateral cerebral ventricle inhibits PEH (9). Depletion of brain serotonin with parachlorophenylalanine also attenuates the blood pressure lowering effect of sciatic stimulation, suggesting involvement of a central serotonergic system (35). Together, these findings support the concept that central mechanisms contribute to the development of PEH, although the specific role of each receptor system and the specific site of interaction are still unresolved.

There is, however, compelling evidence suggesting a crucial role for the central baroreflex pathway in PEH. Disturbance of inputs from the cardiopulmonary and arterial baroreflex to the CNS prior to exercise attenuates the development of PEH. Blocking the cardiac afferents and efferent fibers with intrapericardial procainamide prevents PEH, while blocking the cardiac efferent alone has no effect (8). Similarly, removal of the arterial baroreflex afferents by sinoaortic denervation prevents development of PEH in SHRs (4). These data demonstrate the importance of a functioning baroreflex for expression of PEH. Given that sympathetic nerve activity is reduced after exercise (13,19) rather than elevated, as might be expected during the lower blood pressure, baroreflex-mediated regulation of the sympathetic nerve activity must be reset to a lower operating point during PEH.

CENTRAL BAROREFLEX NETWORK

Resolving the central mechanisms mediating PEH rests on a basic understanding of the central baroreflex network (Fig. 1). In the primary arc of the central baroreflex network, the first central synapse between the primary baroreceptor afferent fibers and second-order neurons is excitatory and is located in the nucleus tractus solitarii (NTS). Within the NTS, the primary excitatory neurotransmitter is glutamate, acting at the ionotropic glutamate receptors to mediate fast synaptic transmission (2). The major inhibitory neurotransmitter is γ-aminobutyric acid (GABA), acting at $GABA_A$ receptors to mediate fast inhibitory transmission. Most of the NTS neurons receive tonic GABA inputs from either interneurons in the NTS or projections from other brain regions (24). Ultimately, the balance of excitatory and inhibitory synaptic inputs shapes the net NTS output of the baroreceptor signals to distal synapses in the central network to coordinate sympathetic nerve activities (24).

In the central network between somatic and baroreflex signaling in blood pressure regulation, afferent fibers from contracting muscles project to the dorsal horn of the spinal cord. Neurons in the dorsal horn of the spinal cord convey these signals to the NTS via the spinosolitary tract. It is becoming recognized that these ascending fibers carrying information from the muscles terminate and release substance P in close proximity to the GABAergic interneurons in the NTS (28).

The NTS output neurons convey signals from the baroreceptor and muscle afferent to neurons in the caudal ventral lateral medulla (CVLM) via excitatory glutamatergic synapses. The neuronal output of the CVLM provides the major inhibitory (GABAergic) inputs to the cardiovascular sympathetic neurons in the rostral ventral lateral medulla (RVLM), the major output neurons projecting to the sympathetic pre-ganglionic neurons in the intermedial lateral cell column in the spinal cord. Thus, within normal baroreflex function, increases in blood pressure activate the baroreceptors, which increase NTS neuronal activity, in turn increasing GABAergic neuronal activity in the CVLM, resulting in decreased firing of the RVLM neurons and decreased sympathetic nerve activity, which returns blood pressure to the control level.

ROLE OF NTS IN PEH

The NTS is the first central site that receives and integrates signals from both baroreceptors and muscles, two key elements in the development of PEH. The NTS is thus an ideal site for integrating cardiovascular responses to exercise.

Substance P mechanism in PEH

Substance P has been under extensive investigation as a neuromodulator or neurotransmitter in the NTS. Considerable evidence suggests that both baroreceptor afferent fibers and skeletal muscle afferent fibers synthesize and release substance P (30–31). Importantly, substance P released from muscle afferent fibers plays a crucial role in cardiovascular responses to exercise (exercise pressor response). Electrically evoked muscle contraction increases blood pressure and attenuates arterial baroreflex function (34). Blocking substance P release in the NTS by microinjections of a substance P antisense oligonucleotide significantly attenuates the exercise pressor response induced by isometric muscle contraction (34). Although all subtypes of the substance P neurokinin receptors are expressed in the NTS, the exercise pressor response appears to be mediated by the neurokinin-1 receptor (NK-1R) subtype. Deleting the NK-1R-expressing neurons in the NTS abolishes the depressive effect of somatic afferent activation on arterial baroreflex function (29).

Given the role of substance P NK-1R in blood pressure regulation during exercise, could substance P NK-1R also contribute to the post-exercise drop in blood pressure? Our laboratory found, in a conscious animal model, that a single bout of treadmill running (at 15 m/min, 10° incline, for 40 min) decreases the mean arterial blood pressure after exercise in SHRs by about 25 mmHg (7,17). Microinjection of a substance P NK-1R antagonist into the NTS before exercise blocks the exercise pressor response and attenuates PEH by 37%, while having no effect on the pre-exercise blood pressure level (7). The data suggest that while basal release of substance P at rest may not play an important role in blood pressure regulation, additional substance P release from exercising muscle afferent fibers and its action in the NTS are important for expression of both exercise pressor response and postexercise hypotension.

GABA mechanisms in PEH

Substance P in the NTS plays a major role as a neuromodulator, by interacting with other fast synaptic transmissions to regulate reflex function (6,16). Could exercise-induced substance P release reset blood pressure by shifting the synaptic excitability in the NTS through its

interaction with GABAergic synaptic transmission? During exercise, activation of muscle afferent fibers elevates blood pressure by stimulating NTS inhibitory interneurons (10–11). Similarly, blocking GABAergic transmission in the NTS prevents the depressed baroreflex function produced by somatic afferents (27). Boscan and colleagues showed that either substance P NK-1R or $GABA_A$ receptor antagonist could block depression of baroreflex function produced by somatic afferent activation (28). The data suggest that activation of the NK1-R by substance P released from muscle afferent fibers enhances inhibitory transmission in the NTS during exercise.

Using the whole cell patch clamp technique, we recorded inhibitory synaptic inputs to NTS second-order baroreceptive neurons after a single bout of dynamic or sham exercise (5). The baroreceptor afferent fibers (aortic depressor nerve) were labeled with a fluorescent dye that can be retrogradely transported to the center terminals. We recorded spontaneous GABAergic inhibitory postsynaptic currents (sIPSCs) from the second-order baroreceptive neurons identified via their fluorescent boutons. The sIPSCs frequency is lower in the SHRs after treadmill exercise (15 m/min, 10° incline, 40 min), compared with that from the sham exercised group (Fig. 2). There is no change in the sIPSC amplitude. The data suggest that inhibitory input to the baroreceptor neurons decreases during PEH. Furthermore, incubation with the substance P NK-1R antagonist has no effect on sIPSC frequency in the PEH group, but significantly decreases the sIPSC frequency in the sham group (Fig. 2). The data suggest that the decrease in inhibitory input to the NTS second-order baroreceptive neurons during PEH involves substance P NK-1R mechanism(s).

Our finding of decreased inhibitory transmission in the NTS during PEH fits into the overall role of GABA signaling in blood pressure regulation under physiological and pathological conditions. It is relevant that an enhanced GABA inhibition in the NTS has been implicated as contributing to the development of hypertension (22). PEH may be more prominent in hypertensive individuals because of reduced GABA release in the NTS after exercise against the background of greater GABA inhibition in hypertension (18).

Substance P – GABA interaction in PEH

How might substance P released from muscle afferent fibers during exercise enhance inhibitory transmission during exercise AND decrease inhibitory transmission during PEH? In general, postsynaptic activation of substance P receptors increases neuronal excitability by depolarizing the resting membrane potential, and decreasing the action potential threshold. Activation of the presynaptic substance P receptors results in a decrease in neurotransmitter release. The source and conditions under which substance P is released may determine the extent to which the presynaptic and postsynaptic mechanisms are integrated to shape neuronal NTS output (6). The increase in inhibitory transmission induced by substance P in the NTS during exercise (28) is consistent with its excitatory role on the soma/dendrites of the GABA interneurons.

During PEH, the reduced sIPSC frequency could be mediated by the NK1-R located on cell soma/dendrites to reduce action potential-mediated transmitter release and/or by the NK1-R located on the terminals to change the spontaneous (action potential-independent) transmitter release. Convincing evidence from our laboratory suggests that exercise-induced internalization of the NK-1R located on the soma/dendrites reduces inhibitory input to the second-order baroreceptive neurons in the NTS (5). First, in the presence of tetrodotoxin, which blocks action potential generation, the miniature IPSC (mIPSC) frequency from SHRs in the PEH group did not differ from those of the sham group. The data suggest that the reduced inhibitory transmission is unlikely due to the inhibitory role of substance P acting on the GABA terminals to reduce GABA release. Second, exogenous substance P elicits a significantly greater increase in sIPSC frequency in the sham group compared with the PEH group, suggesting down-regulation of substance P NK-1R during PEH. Since exogenous substance P

does not consistently affect the mIPSC frequency, the data is consistent with down-regulation of the NK1-R located on the soma/dendrites. Finally, double labeling of NK1-R and glutamic acid decarboxylase (GAD 67, a marker for GABA neurons) shows that GABA neurons have a higher degree of NK-1R internalization during PEH (Fig. 3). The neuron from the sham group (figure 3A1) shows a distinct ring of NK1-R staining on the surface of the neuron. This was confirmed by plotting the fluorescent intensity across the neuron (Fig. 3B1), the peak NK-1R fluorescent intensity was outside of the GAD 67 fluorescent intensity. The neurons from the PEH group show a high degree of overlapping staining for NK-1R and GAD 67 (Fig. 3A2 and 3B2).

Together, the data suggest that activation of NK-1R during exercise results in NK-1R internalization to reduce inhibitory transmission in the NTS after exercise, and thus PEH. This reduced inhibitory influence on the second-order baroreceptive neurons is expected to increase NTS output to downstream neurons in the CVLM, resulting in greater inhibition in the RVLM (figure 1).

ROLE OF RVLM IN PEH

Decreased sympathetic nerve activity is the most salient feature of PEH, implicating the involvement of cardiovascular vasomotor neurons located in the RVLM (13,19). Cardiovascular reflex-mediated and descending modulations of the sympathetic activity are relayed through neurons in the RVLM, characterized by their sympathetic related rhythm and cardiac rhythm from entrainment by baroreceptor input (15,17). As in the NTS, the activities generated by these RVLM neurons are determined by the balance of excitatory and inhibitory synaptic influences. Glutamate is the major excitatory neurotransmitter, while GABA acting at $GABA_A$ receptors largely provides the tonic inhibition. A shift in the synaptic balance toward inhibition, such as activation of $GABA_A$ receptors, results in a decrease in baseline activity of RVLM neurons and, consequently, a decrease in sympathetic nerve activity and blood pressure (23). A shift in the synaptic balance toward excitation, such as in animal models of hypertension, increases sympathetic nerve activity and blood pressure (32).

Can exercise shift the balance of synaptic excitability in RVLM towards inhibition to reduce sympathetic output, and hence induce PEH? We explored this possibility by studying SHRs after a single bout of dynamic exercise (treadmill running at 15 m/min, 10° incline for 40 min) (17). We identified the cardiovascular sympathetic neurons in RVLM by their temporal relationship to lumbar sympathetic nerve activity (LSNA) and cardiac rhythm. These cardiovascular sympathetic neurons in RVLM had significantly lower spontaneous firing activity (figure 4), along with reduced LSNA and blood pressure in the PEH group compared with the sham group. The data suggest that reduced sympathetic nerve activity during PEH is mediated by a reduced central output from RVLM. Furthermore, the $GABA_A$ receptor antagonist, bicuculline, increases RVLM neuronal firing activity, and the increase is greater in neurons in the PEH group compared with the sham group (Fig. 4). The data suggest that shifting the synaptic balance to inhibition by up-regulating GABA signaling at RVLM cardiovascular sympathetic neurons leads to decreased neuronal output after exercise.

Up-regulation of GABA signaling in RVLM may be due to neuroplasticity within the RVLM and/or from upstream regions. A number of neuromodulators (*e.g.*, opioid, serotonin, angiotensin II, and nitric oxide) alter the RVLM neuronal output to modulate cardiovascular responses during exercise (1,33). Given that these cardiovascular sympathetic neurons in RVLM receive the majority of the GABA inputs from upstream nuclei in the baroreflex pathway and that these neurons relay the baroreflex-mediated responses generated from upstream nuclei (Fig. 1), neuroplasticity in upstream regions (such as changes in the NTS output) is likely to contribute to reduced activity in the RVLM.

PROPOSED MODEL

Within the NTS, blood pressure information is first processed and the balance of excitatory and inhibitory synaptic transmissions shapes the baroreflex output from the NTS to down-stream synapses. During exercise, muscle afferent fibers release substance P in the NTS. The action of substance P is localized to excite the GABA inhibitory interneurons, leading to increased GABA release in the NTS (Fig. 5). As a result, there is reduced NTS output and the blood pressure resets to a higher level (exercise pressor response). Subsequently, binding of substance P to the NK1-R triggers the receptor to undergo internalization, which reduces GABA interneuron excitability after exercise, resulting in reduced GABA inhibition in the NTS. Disinhibition of the NTS neurons in the baroreflex pathway could translate to a higher excitatory output from NTS to CVLM and a greater inhibition to the RVLM. Lower RVLM neuronal output translates to lower sympathetic nerve activity, and hence, lower blood pressure after exercise.

FUTURE CHALLENGES

The current data suggest that exercise-induced NK1-R down-regulation to reduce GABA inhibitory input to baroreceptor second-order neurons can provide the first line of neuroplasticity in NTS for lowering blood pressure after exercise. However, full expression of PEH is likely mediated by several mechanisms from short- to long-term changes and peripheral to central nervous system effects. Remaining issues include what is the nature of the interaction between the changes in medulla neuronal activities to other previously reported neuromodulators, such as vasopressin, opioids, and serotonin? Are these mechanisms interactive or redundant? What is the contribution from other higher brain regions in the expression of PEH? What are the cellular mechanisms mediating the changes in neuronal activities (*e.g.*, receptor trafficking, receptor phosphorylation and/or dephosphorylation, changes in gene expression or post-translational modification)? More studies are needed to better understand the development and expression of PEH.

CONCLUSION

Recent findings from our laboratory (5,7,17) and other's (28) in exercise and blood pressure regulation have uncovered an elegant interaction between substance P and the GABAergic system in the NTS that contributes to both the exercise pressor response and PEH. During exercise, muscle afferent fibers release substance P to activate a specific group of GABA interneurons in the NTS to reset the baroreflex to a high blood pressure (exercise pressor response). Consequently, activation of substance P NK1-R during exercise triggers receptors internalization and results in prolonged disinhibition on the second-order baroreceptive neurons in the NTS. Disinhibition of the baroreceptor neurons in the NTS translates, via activation of the GABAergic neurons in the CVLM, to greater RVLM inhibition resulting in lower blood pressure (PEH).

Summary

Our studies suggest that exercise-induced neuroplasticity in the nucleus tractus solitarii and rostral ventral lateral medulla contributes to postexercise hypotension.

Acknowledgments

Current contact information for Dr. Ann C. Bonham: Chief Scientific Officer, Association of American Medical Colleges, 2450 N Street, NW, Washington, DC 20037. The authors gratefully acknowledge Drs. Kayleen Kott, Betty Guo and Jeffrey Elias for editorial assistance.

Funding sources: National Institutes of Health; American Heart Association

References

1. Ally A, Maher TJ. Endothelial NOS expression within the ventrolateral medulla can affect cardiovascular function during static exercise in stroked rats. Brain Res 2008;1196:33–40. [PubMed: 18234158]
2. Baude A, Strube C, Tell F, Kessler JP. Glutamatergic neurotransmission in the nucleus tractus solitarii: structural and functional characteristics. J Chem Neuroanat 2009;38:145–153. [PubMed: 19778680]
3. Boone JB Jr. Corry JM. Proenkephalin gene expression in the brainstem regulates post-exercise hypotension. Brain Res Mol Brain Res 1996;42:31–38. [PubMed: 8915577]
4. Chandler MP, DiCarlo SE. Sinoaortic denervation prevents postexercise reductions in arterial pressure and cardiac sympathetic tonus. Am J Physiol 1997;273:H2738–2745. [PubMed: 9435610]
5. Chen CY, Bechtold AG, Tabor J, Bonham AC. Exercise reduces GABA synaptic input onto nucleus tractus solitarii baroreceptor second-order neurons via NK1 receptor internalization in spontaneously hypertensive rats. J Neurosci 2009;29:2754–2761. [PubMed: 19261870]
6. Chen CY, Joad JP, Bric J, Bonham AC. Central mechanisms I: plasticity of central pathways. Handb Exp Pharmacol 2009:187–201. [PubMed: 18825341]
7. Chen CY, Munch PA, Quail AW, Bonham AC. Postexercise hypotension in conscious SHR is attenuated by blockade of substance P receptors in NTS. Am J Physiol Heart Circ Physiol 2002;283:H1856–1862. [PubMed: 12384463]
8. Collins HL, DiCarlo SE. Attenuation of postexertional hypotension by cardiac afferent blockade. Am J Physiol 1993;265:H1179–1183. [PubMed: 8238403]
9. Collins HL, Rodenbaugh DW, DiCarlo SE. Central blockade of vasopressin V(1) receptors attenuates postexercise hypotension. Am J Physiol Regul Integr Comp Physiol 2001;281:R375–380. [PubMed: 11448838]
10. Degtyarenko AM, Kaufman MP. Barosensory cells in the nucleus tractus solitarius receive convergent input from group III muscle afferents and central command. Neuroscience 2006;140:1041–1050. [PubMed: 16626870]
11. Degtyarenko AM, Kaufman MP. MLR-induced inhibition of barosensory cells in the NTS. Am J Physiol Heart Circ Physiol 2005;289:H2575–2584. [PubMed: 16055517]
12. Fitzgerald W. Labile hypertension and jogging: new diagnostic tool or spurious discovery? Br Med J (Clin Res Ed) 1981;282:542–544.
13. Floras JS, Sinkey CA, Aylward PE, Seals DR, Thoren PN, Mark AL. Postexercise hypotension and sympathoinhibition in borderline hypertensive men. Hypertension 1989;14:28–35. [PubMed: 2737735]
14. Groom D. Cardiovascular observations on Tarahumara Indian runners--the modern Spartans. Am Heart J 1971;81:304–314. [PubMed: 5547429]
15. Guyenet PG, Haselton JR, Sun MK. Sympathoexcitatory neurons of the rostroventrolateral medulla and the origin of the sympathetic vasomotor tone. Prog Brain Res 1989;81:105–116. [PubMed: 2616776]
16. Helke CJ, Seagard JL. Substance P in the baroreceptor reflex: 25 years. Peptides 2004;25:413–423. [PubMed: 15134864]
17. Kajekar R, Chen CY, Mutoh T, Bonham AC. GABA(A) receptor activation at medullary sympathetic neurons contributes to postexercise hypotension. Am J Physiol Heart Circ Physiol 2002;282:H1615–1624. [PubMed: 11959623]
18. Kenney MJ, Seals DR. Postexercise hypotension. Key features, mechanisms, and clinical significance. Hypertension 1993;22:653–664. [PubMed: 8225525]
19. Kulics JM, Collins HL, DiCarlo SE. Postexercise hypotension is mediated by reductions in sympathetic nerve activity. Am J Physiol 1999;276:H27–32. [PubMed: 9887013]
20. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-

Rosett J, Hong Y. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:e21–181. [PubMed: 19075105]

21. Mach C, Foster C, Brice G, Mikat RP, Porcari JP. Effect of exercise duration on postexercise hypotension. J Cardiopulm Rehabil 2005;25:366–369. [PubMed: 16327532]
22. Mei L, Zhang J, Mifflin S. Hypertension alters GABA receptor-mediated inhibition of neurons in the nucleus of the solitary tract. Am J Physiol Regul Integr Comp Physiol 2003;285:R1276–1286. [PubMed: 14615399]
23. Menezes RC, Fontes MA. Cardiovascular effects produced by activation of GABA receptors in the rostral ventrolateral medulla of conscious rats. Neuroscience 2007;144:336–343. [PubMed: 17049168]
24. Mifflin SW. What does the brain know about blood pressure? News Physiol Sci 2001;16:266–271. [PubMed: 11719602]
25. Pescatello LS, Guidry MA, Blanchard BE, Kerr A, Taylor AL, Johnson AN, Maresh CM, Rodriguez N, Thompson PD. Exercise intensity alters postexercise hypotension. J Hypertens 2004;22:1881–1888. [PubMed: 15361758]
26. Polito MD, Farinatti PT. The effects of muscle mass and number of sets during resistance exercise on postexercise hypotension. J Strength Cond Res 2009;23:2351–2357. [PubMed: 19826288]
27. Potts JT. Exercise and sensory integration. Role of the nucleus tractus solitarius. Ann N Y Acad Sci 2001;940:221–236. [PubMed: 11458680]
28. Potts JT. Inhibitory neurotransmission in the nucleus tractus solitarii: implications for baroreflex resetting during exercise. Exp Physiol 2006;91:59–72. [PubMed: 16239249]
29. Potts JT, Fong AY, Anguelov PI, Lee S, McGovern D, Grias I. Targeted deletion of neurokinin-1 receptor expressing nucleus tractus solitarii neurons precludes somatosensory depression of arterial baroreceptor-heart rate reflex. Neuroscience 2007;145:1168–1181. [PubMed: 17293052]
30. Potts JT, Fuchs IE. Naturalistic activation of barosensitive afferents release substance P in the nucleus tractus solitarius of the cat. Brain Res 2001;893:155–164. [PubMed: 11223003]
31. Potts JT, Fuchs IE, Li J, Leshnower B, Mitchell JH. Skeletal muscle afferent fibres release substance P in the nucleus tractus solitarii of anaesthetized cats. J Physiol 1999;514(Pt 3):829–841. [PubMed: 9882754]
32. Sved AF, Ito S, Yajima Y. Role of excitatory amino acid inputs to the rostral ventrolateral medulla in cardiovascular regulation. Clin Exp Pharmacol Physiol 2002;29:503–506. [PubMed: 12010199]
33. Tedesco A, Ally A. Angiotensin II type-2 (AT2) receptor antagonism alters cardiovascular responses to static exercise and simultaneously changes glutamate/GABA levels within the ventrolateral medulla. Neurosci Res 2009;64:372–379. [PubMed: 19379780]
34. Williams CA, Ecay T, Reifsteck A, Fry B, Ricketts B. Direct injection of substance P-antisense oligonucleotide into the feline NTS modifies the cardiovascular responses to ergoreceptor but not baroreceptor afferent input. Brain Res 2003;963:26–42. [PubMed: 12560109]
35. Yao T, Andersson S, Thoren P. Long-lasting cardiovascular depressor response following sciatic stimulation in spontaneously hypertensive rats. Evidence for the involvement of central endorphin and serotonin systems. Brain Res 1982;244:295–303. [PubMed: 6288187]

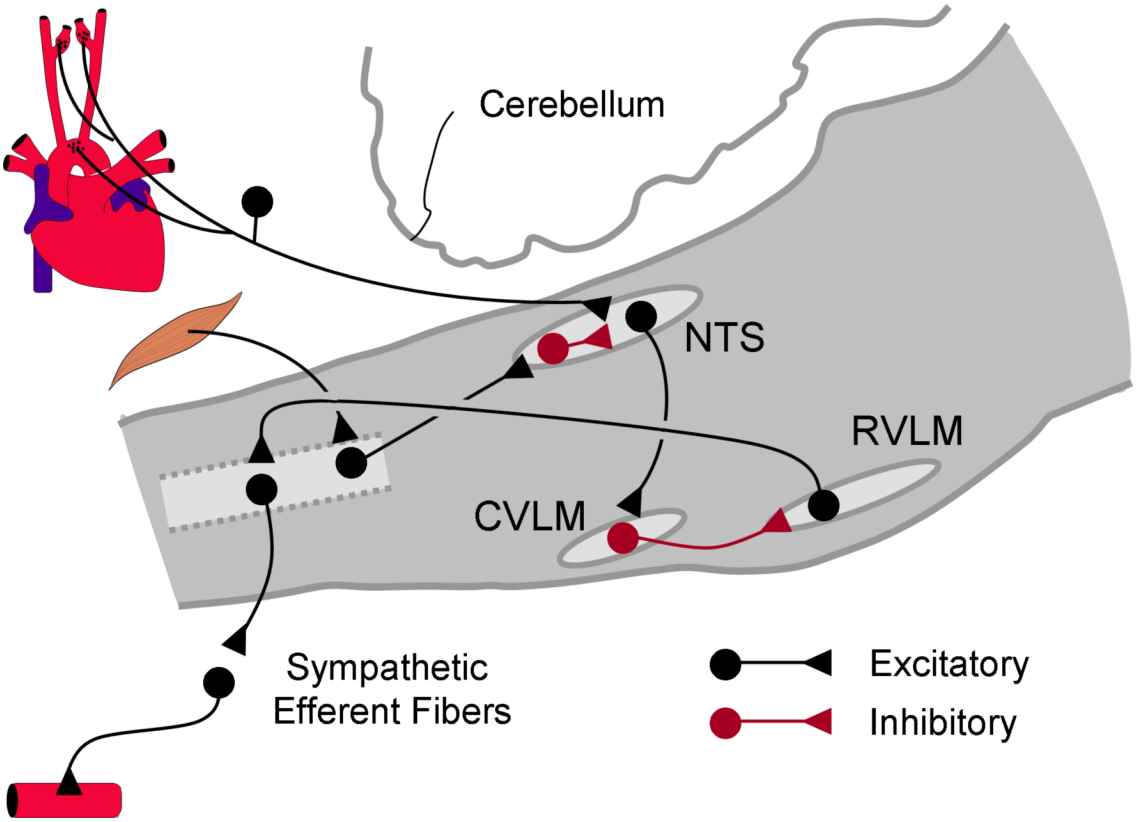

Figure 1.
A simplified schematic illustrating the brainstem baroreflex pathway. The baroreceptor afferent fibers, carrying blood pressure information, make excitatory synaptic contact with second-order neurons in the nucleus tractus solitarii (NTS), the first central site that receives and integrates the sensory inputs. The afferent fibers from skeletal muscle also project to the NTS through a poly-synapse pathway. These ascending fibers carrying information from the muscles make excitatory synaptic contact with the GABAergic interneurons in the NTS. The NTS output neurons convey signals from the baroreceptors and muscle afferents to neurons in the caudal ventral lateral medulla (CVLM) via excitatory glutamatergic synapses. The neuronal output of the CVLM provides the major inhibitory (GABAergic) inputs to the cardiovascular sympathetic neurons in the rostral ventral lateral medulla (RVLM), the major output neurons that regulate sympathetic nerve activity.

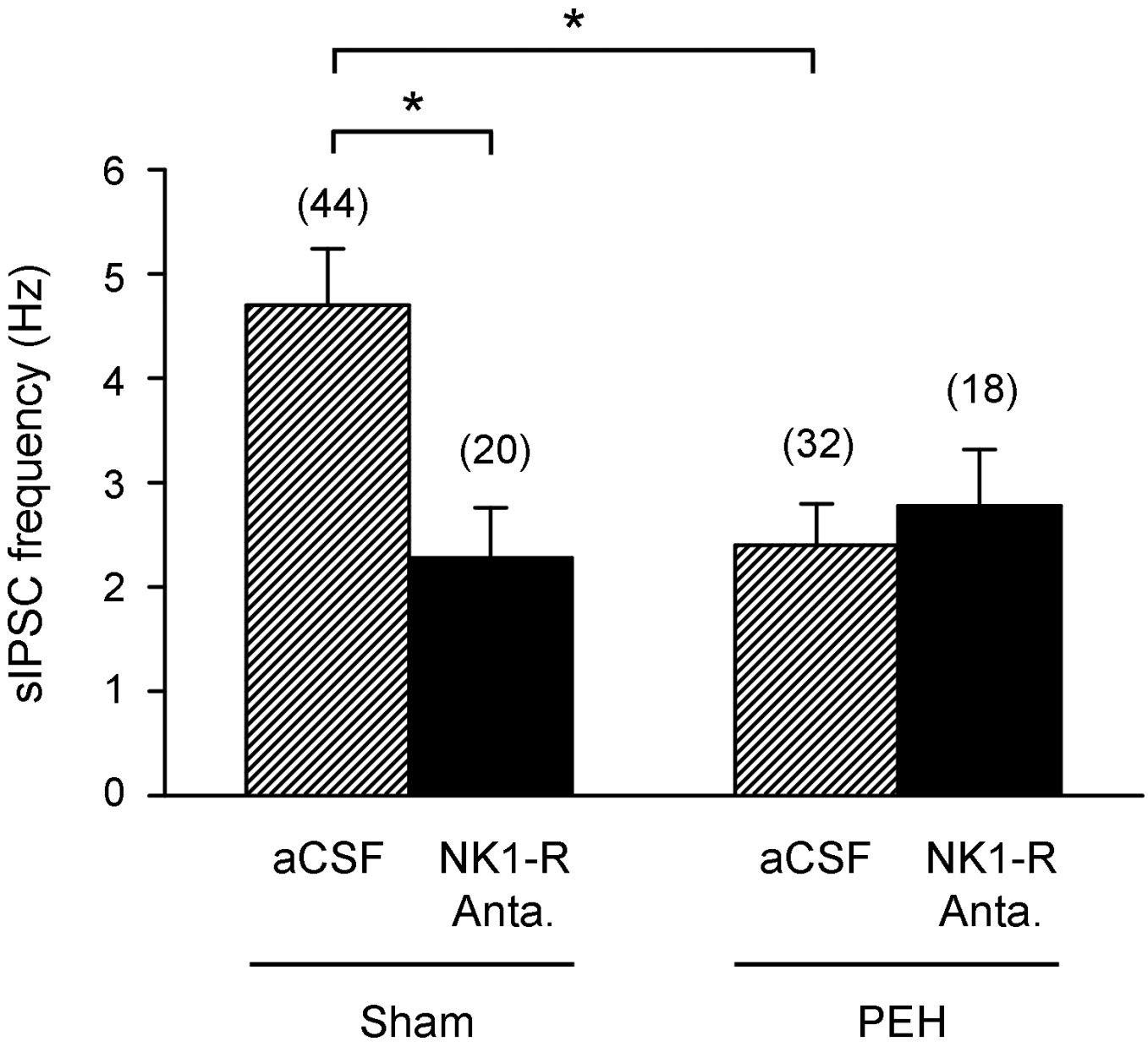

Figure 2.

A single bout of dynamic exercise decreases the frequency of spontaneous inhibitory postsynaptic currents (sIPSC) recorded from second-order baroreceptive nucleus tractus solitarii (NTS) neurons in spontaneously hypertensive rats. Incubation with neuronkinin-1 receptor (NK1-R) antagonist significantly reduces the sIPSC frequency in the sham but not the postexercise hypotension (PEH) group. Numbers in parentheses indicate number of neurons. * $p<0.05$, Fisher's LSD test. [Adapted from Chen C-Y, Bechtold AG, Tabor J, Bonham AC. Exercise reduces GABA synaptic input onto nucleus tractus solitarii baroreceptor second-order neurons via NK1 receptor internalization in spontaneously hypertensive rats. J. Neurosci. 2009; 29(9):2754-2761. Copyright © 2009 Society for Neuroscience. Used with permission.]

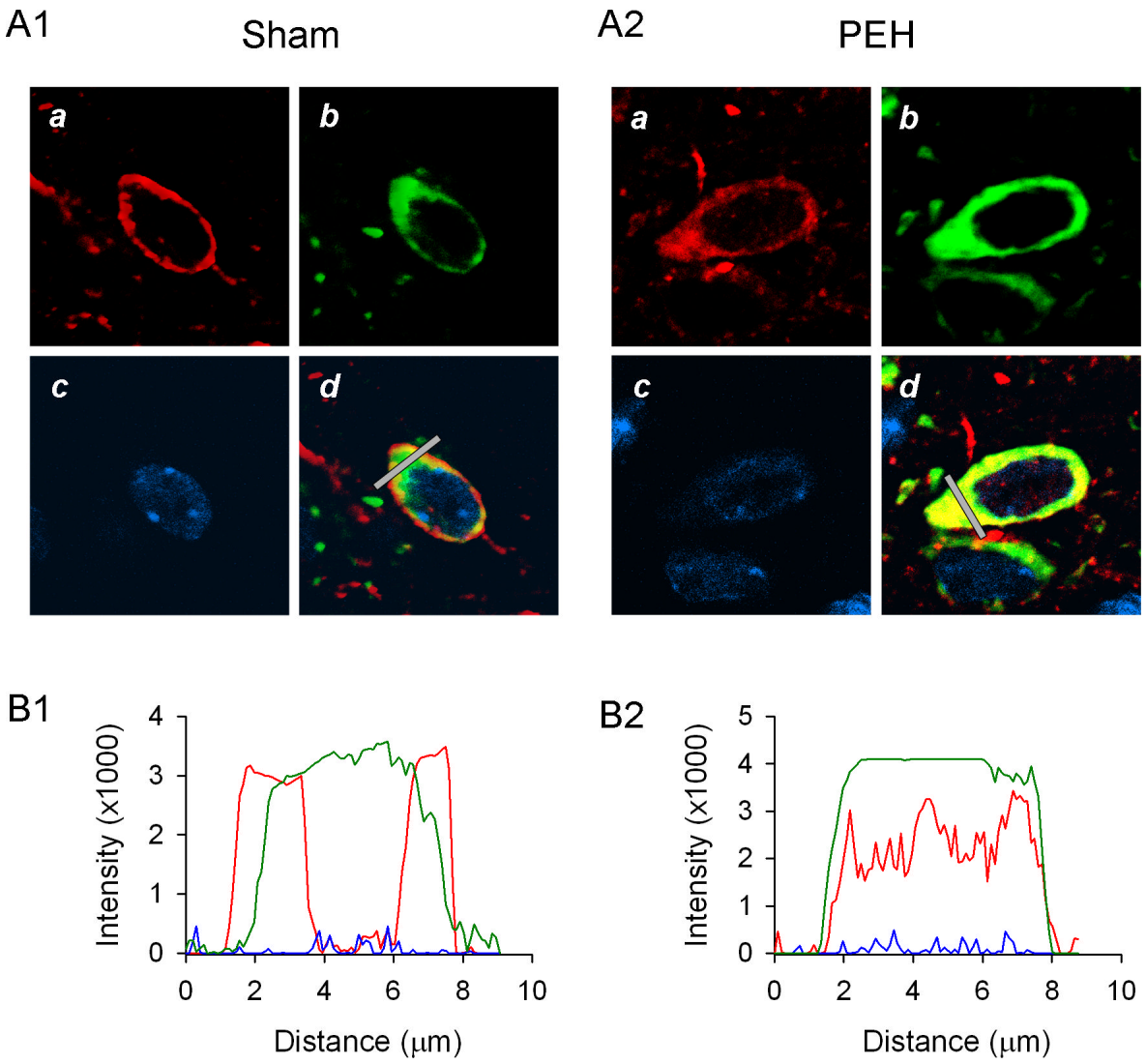

Figure 3.

A. Example images from one sham (A1) and one postexercise hypotension (PEH) (A2) rat. ***a***, neuronkinin-1 receptor (NK1-R) staining (red color). ***b***, glutamic acid decarboxylase (GAD 67) staining (green color). ***c***, SYTOX staining (blue color). ***d***, Overlap of a, b, and c. B. Fluorescent intensity plot across the white lines in A1***d*** and A2***d.*** PEH is associated with a higher degree of NK1-R internalization on nucleus tractus solitarii (NTS) γ-aminobutyric acid (GABA) neurons. [Adapted from Chen C-Y, Bechtold AG, Tabor J, Bonham AC. Exercise reduces GABA synaptic input onto nucleus tractus solitarii baroreceptor second-order neurons via NK1 receptor internalization in spontaneously hypertensive rats. J. Neurosci. 2009; 29(9): 2754-2761. Copyright © 2009 Society for Neuroscience. Used with permission.]

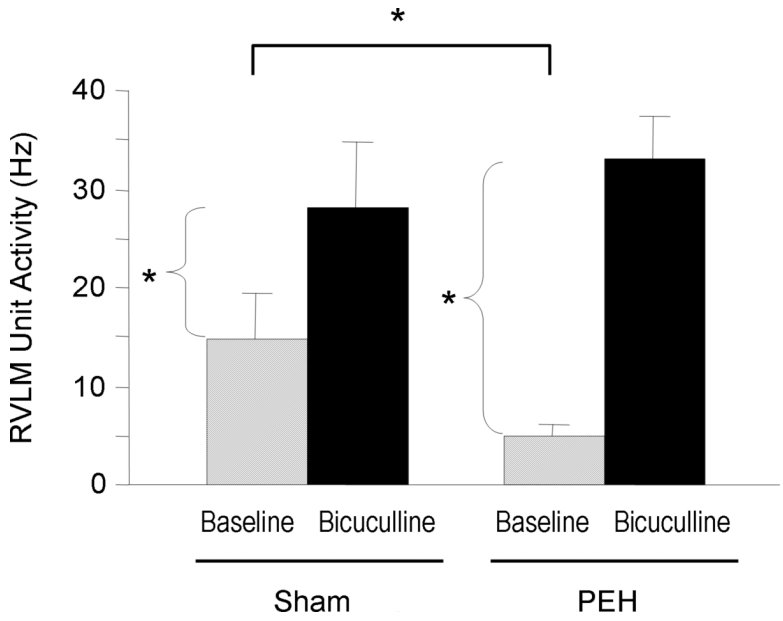

Figure 4.

Group data showing bicuculline-induced maximal increases in rostral ventral lateral medulla (RVLM) neuronal activity in postexercise hypotension (PEH) and sham groups. The maximal bicuculline-induced increase in RVLM neuronal firing activity (closed bars) over the baseline firing activity (open bars) is significantly greater in neurons in the PEH group compared to the sham group. Resting unit activity is significantly lower in PEH compared to sham. Maximal unit activity is not significantly different between the two groups. [Adapted from Kajekar R. Chen C-Y, Mutoh T, Bonham AC. $GABA_A$ receptor activation at medullary sympathetic neurons contributes to postexercise hypotension. Am J Physiol Heart Circ Physiol. 2002; 282:H1615–H1624. Copyright © 2002 the American Physiological Society. Used with permission.]

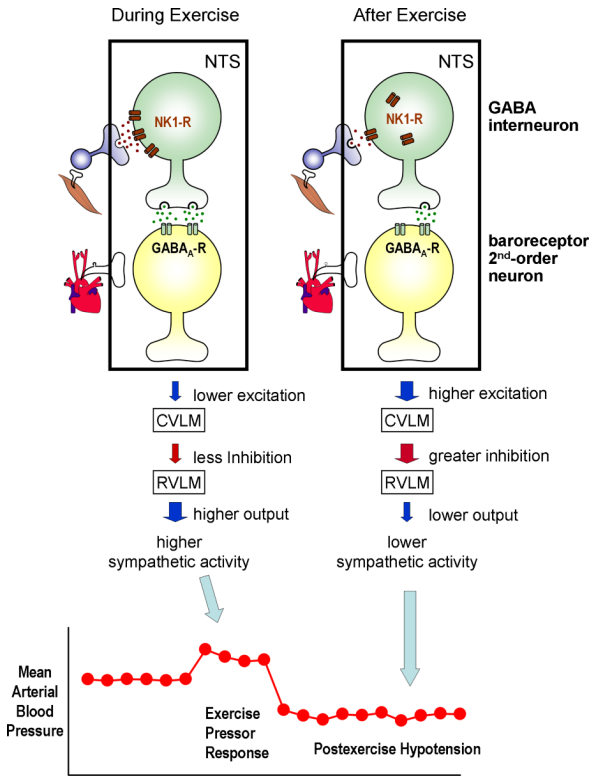

Figure 5.

A simplified schematic illustrating the interaction between substance P and γ-aminobutyric acid (GABA) transmissions in the nucleus tractus solitarii (NTS) on blood pressure regulation before, during and after exercise. During exercise, muscle afferent releases substance P to activate the NTS GABA interneurons to reset baroreflex to a higher level (exercise pressor response). Activation of the neurokinin-1 receptor (NK1-R) during exercise triggers the receptor to undergo internalization, which dampens the NTS GABA interneurons and resets baroreflex to a lower level after exercise (postexercise hypotension). [Adapted from Chen C-Y, Bechtold AG, Tabor J, Bonham AC. Exercise reduces GABA synaptic input onto nucleus tractus solitarii baroreceptor second-order neurons via NK1 receptor internalization in spontaneously hypertensive rats. J. Neurosci. 2009; 29(9):2754–2761. Copyright © 2009 Society for Neuroscience. Used with permission.]