

Mini review

Neural mechanisms and post-exercise hypotension: The importance of experimental studies

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Abstract— A single bout of exercise can decrease blood pressure level in hypertensive individuals and this phenomenon is known as post-exercise hypotension (PEH). PEH is clinically important and reduces blood pressure after physical exercise in hypertensive subjects. This reduction has been attributed to autonomic mechanisms, e.g., reduced peripheral sympathetic activity, adjustments in cardiac autonomic balance and baroreflex sensitivity. Besides, evidence has suggested that the central baroreflex pathway has an important role in the occurrence of PEH. Therefore, the aim of this study was to review the effects of physical exercise on areas of the central nervous system involved in the regulation of blood pressure.

Keywords: central nervous system, post-exercise hypotension, mechanisms.

Introduction

Systemic hypertension is a multifactorial clinical condition and an independent risk factor for mortality in patients with cardiovascular diseases¹. Increase in blood pressure is linked to neural mechanisms, e.g., autonomic dysfunction, sympathetic hyperactivity and disarray in arterial baroreceptors and chemoreceptors^{2,3,4}. The arterial baroreceptor in hypertensive subjects adapts to high levels of blood pressure, via receptors depolarization reduction, diminishing thus its functional capacity^{5,6}.

The role of physical exercise in blood pressure reduction has been well documented in animal models⁷ and humans^{8,9}, and this phenomenon occurs due to adjustments in the neurohumoral mechanisms. Post-exercise hypotension [PEH] is a prolonged decrease in arterial blood pressure after a single bout of exercise⁷.

The autonomic mechanisms attributed to PEH are well-documented, such as reduced peripheral sympathetic activity^{10,11}, modifications in the cardiac autonomic activity^{12,13} and adjustments in the baroreflex sensitivity^{14,15}. On the other hand, the central neural mechanisms have only recently been discovered and investigated. This review emphasizes on evidence of synaptic mechanisms in the central baroreflex pathway that contribute to development of PEH. Therefore, we will summarize studies that define important areas of central nervous system (CNS) involved in physical activities and blood pressure regulation.

Central baroreflex arc, blood pressure, and sympathetic activity

Regulation of the cardiovascular system by the baroreflex involves multiple components of the baroreflex arc, such as sensors (baroreceptors), afferents pathway (depressor nerve aortic), central circuit (nucleus tractus solitarius (NTS) and others brain areas), and efferent pathway (heart, vessels). The afferent fibers baroreceptor, which carries blood pressure information, makes an excitatory

synaptic contact with second-order neurons in the NTS. The NTS integrates and receives information from arterials baroreceptors and through connections with caudal ventral lateral medulla (CVLM), rostral ventral lateral medulla (RVLM), and dorsal nucleus of the vagus nerve promotes the control of hemodynamics to adjust blood pressure¹⁶. Within the NTS, glutamate, a primary excitatory neurotransmitter, acts on ionotropic glutamate receptors to mediate fast synaptic transmission¹⁷. The afferent fibers from skeletal muscle also project the NTS through a poly-synapse pathway. These ascending fibers, which carry information from the muscles, make an excitatory synapse releasing the substance P closer to the GABAergic interneurons in the NTS¹⁸. The NTS output neurons convey signals from the baroreceptors and muscles afferent to neurons in the CVLM via excitatory glutamatergic synapses. The neuronal output of the CVLM provides inhibitory (GABAergic) inputs to the cardiovascular sympathetic neurons in the RVLM, projecting to the sympathetic pre-ganglionic neurons in the intermediolateral cell column in the spinal cord. Therefore, increase in blood pressure activate the baroreceptors, which increases NTS neuronal activity, increasing GABAergic neuronal activity in the CVLM, which decreases neurons activity of the RVLM and reduces the sympathetic nerve activity that returns blood pressure to the control level.

Blood pressure is determined by product of vascular peripheral resistance with cardiac output, and efferent pathways of sympathetic vasomotor outflow control both determinants factors. This sympathetic outflow presents tonic activity and has source in intermediolateral cell column in preganglionic neurons located in the spinal cord. Moreover, this sympathetic tone activity controls the cardiovascular function through vasoconstrictors and cardioaccelerator adjustments¹⁹.

Direct projections of the intermediolateral column originates predominantly from at least five areas of the brain: a) rostral ventrolateral medulla (RVLM); b) rostral ventromedial medulla; c) caudal raphe nuclei; d) A5 cell group in the pons; and e) paraventricular nucleus of the hypothalamus (PVN). The

RVLM has a great relevance in sympathetic regulation to the cardiovascular system and PVN may provide a tonic excitatory drive to the RVLM neurons. PVN neurons send direct projections to sympathetic preganglionic neurons of the intermediolateral column²⁰, therefore, PVN neurons can affect the sympathetic tonus through its direct and indirect connections. Consequently, both RVLM and PVN could adjust sympathetic vasomotor tone and regulates blood pressure^{21,22,23}.

Post-exercise hypotension

Post-exercise hypotension (PEH) has been observed in normotensive and hypertensive humans^{8,9}, likewise, in animal models of hypertension⁷, being greater in hypertensive than normotensive subjects^{24,25,26}. In humans, PEH has been documented following various types of dynamic exercise (walking, running, cycling, and swimming), as well as in resistance exercise^{7,25,26,27,28}.

The duration of PEH occurs from ten minutes and persists until 24 hours after a bout of exercise^{29,30}. Different methods have been used to assess it, such as the auscultatory method^{31,32}, intra-arterial measurement method^{33,34}, and ambulatory blood pressure monitoring (24h assessment)^{29,30,31,35}. In the recent meta-analysis, Cassonato et al.⁸ showed that a single bout of resistance exercise elicited small-to-moderate reductions in systolic blood pressure at 60 and 90 minutes after exercise, and in 24-hour ambulatory blood pressure compared to control session. They concluded that a single bout of resistance exercise could have a blood pressure-lowering effect that lasts up to 24 hours. Marques-Silvestre et al.⁹ found in their systematic review, relevant reductions of systolic/diastolic blood pressure after a session of dynamic aerobic exercise and it was maintained for

several hours. Therefore, these post-exercise blood pressure reductions could have an impact on cardiovascular health, since a 5 mm Hg reduction is clinically significant and is associated with risk reduction for stroke and heart disease of 15%–20%³⁶. Also, it is interesting to note that the time and magnitude of PEH depends on the subject's characteristics³⁷, physical activity type^{34,38}, muscle mass involved³⁹, duration, volume and/or intensity of physical activity performed^{25,40,41,42}.

The use of physical exercise to reduce blood pressure in hypertensive subjects is already well emphasized in clinical trials and systematic reviews^{8,43,44,45}. In addition, several clinical trials identified the effectiveness of physical training to reduce blood pressure levels^{46,47,48}, as well as in meta-analysis^{7,49,50,51}. Meta-analysis of Halbert et al.⁵¹ published for two decades, showed reductions of – 4.7mmHg and – 3.1mmHg in systolic and diastolic blood pressure, respectively. Fagard⁴⁹ identified reductions of – 3.3 mmHg in systolic blood pressure and – 3.5 mmHg in diastolic blood pressure. Similarly, Whelton et al.⁵⁰ observed a significant reduction in systolic and diastolic blood pressure of – 3.84 mmHg and – 2.58 mmHg, respectively.

It is known that neural mechanisms are associated with PEH, such as reduction of sympathetic nervous activity, increase of vagal modulation, and improved baroreflex sensitivity^{10,11,26,46}. In table 1 are presented post-exercise autonomic responses assessed by different methods. Overall, there were reductions of muscle sympathetic nerve activity after aerobic exercise^{10,11,52}, reduction of cardiac autonomic balance^{14,53}, and increase of baroreflex sensitivity and heart rate variability⁵⁴. Contrarily, other studies reported increased cardiac and vasomotor sympathetic modulation, decreased parasympathetic modulation and/or attenuation of baroreflex sensitivity^{12,13,15,55} however, those studies used resistance exercise^{13,15,55} or maximal aerobic exercise¹².

Table 1. The effect of physical exercise on autonomic and hemodynamic parameters.

Author	Subjects/Protocol	Responses	
		Hemodynamic	Autonomic
Aprile et al. ⁵²	9 patients with stages 2-3 chronic kidney disease (50 ± 8 years) and 12 healthy volunteers (50 ± 5 years) Randomized sessions: (1) exercise (45 min, cycle ergometer, 50% of VO2peak) and (2) rest (seated, 45 min).	Both groups ↓SBP, ↓DAP, ↓FVR.	Both groups ↓MSNA
Trevizani et al. ⁵³	9 hypertensive men (HT: 58.0 ± 7.7 years) and 11 normotensive men (NT: 57.1 ± 6.0 years) (1) resistance exercise session (two sets of 15–20 repetitions, 50% of 1RM, 120 s intervals between sets/exercise)	-	In HT and NT ↓SM, ↓PM, ↓SDNN, ↓pNN50, ↓RMSSD, ↓AB
Liu et al. ¹⁴	17 prehypertensive, (45 – 60 years). (1) aerobic exercise session and (2) aerobic training 8-week (four times per week, 30 min per session, 65% VO2max).	Acute exercise ↓BP After 8-wk ↓BP	After 8-week ↓AB
Queiroz et al. ⁵⁵	12 hypertensives (HT) and 14 normotensives (NT) (1) resistance exercise sessions (seven exercises, three sets, 50% – 1RM) and control session (rest)	In HT and NT ↓SBP, ↓DAP, ↓SV, ↑HR, ↔CO, ↔SVR	In HT and NT ↑AB

Author	Subjects/Protocol	Responses	
		Hemodynamic	Autonomic
Niemela et al. ¹⁵	12 healthy male subjects. (31 ± 3 years) Randomized sessions: (1) aerobic exercise session on a bicycle, (2) light resistance exercise session, (3) heavy resistance exercise session, and (4) control intervention with no exercise.	-	After 30 and 60 min (aerobic and light resistance exercise) ↓BRSLF After heavy exercise ↓PM, ↑SM-SBP
Resk et al. ¹³	17 normotensives Experimental sessions: (1) control (C-40 min of rest), (2) low – (E40% – 1RM), and (3) high-intensity (E80% – 1 RM) resistance exercises.	After E40% ↓SBP, ↓DBP, ↔SVR, ↓SV, ↑HR, ↓CO After E80% ↔DBP, ↓SV, ↑SVR, ↑HR, ↓CO	After E40% and E80% ↑SM, ↓PM,
Bisquolo et al. ¹⁰	21 healthy young men Randomized sessions: (1) aerobic exercise session on a bicycle (50% VO2peak) and (2) control session.	Between sessions ↔BP, ↔HR Exercise session ↑FBF	Exercise session ↓MSNA
Raczak et al. ⁵⁴	18 healthy males (20 – 24 years) (1) aerobic exercise session on a treadmill for 30 min at 65% – maximal HR.	↓SBP	↑BS, ↑SDNN, ↔HRV
Halliwill, Taylor and Eckberg ¹¹	9 healthy subjects (22 – 27 years) (1) aerobic exercise session on a bicycle, 60 min at 60% VO2peak or (2) control session (60 min seated rest).	↓SBP, ↓MBP, ↓TPR, ↑CO.	↓MSNA
Piepoli et al. ¹²	10 normal subjects Randomized sessions: (1) aerobic exercise (maximal upright bicycle) and (2) control session (no exercise day, 30 min of upright rest)	After 60min ↓DBP, ↑CO, ↔SV, ↓SVR	After 60min ↑SM, ↓PM, After 10min ↓BS

Abbreviations: SBP, systolic arterial pressure; DBP, diastolic arterial pressure; MBP, mean arterial pressure; MSNA, muscle sympathetic nerve activity; TPR, total peripheral resistance; CO, cardiac output; VO2peak, peak oxygen uptake; VO2max, maximum oxygen consumption; FVR, forearm vascular resistance; FBF, forearm blood flow; SV, stroke volume; SVR, systemic vascular resistance; BS, baroreflex sensitivity; SM, sympathetic modulation; PM, parasympathetic modulation; AB, autonomic balance; RM, repetition maximum; BRSLF, baroreflex sensitivity of low frequency band; SM-SAP, sympathetic modulation of systolic arterial pressure; SDNN, standard deviation of normal-to-normal RR intervals; HRV, heart rate variability; pNN50, duration higher than 50 ms in relation to the total number of normal RR intervals; RMSSD, square root of the mean square differences of successive normal-to-normal RR intervals; ↓ decrease; ↔ no change; ↑ increase.

Neural mechanisms and PEH

The hemodynamic changes induced by physical exercise depends on cardiovascular autonomic activity and CNS. Regarding the areas of CNS, studies have shown that the RVLM^{56,57}, NTS^{58,59}, and PVN^{58,60,61} are involved with this cardiovascular control.

Evidence has shown that there are important mechanisms working in the nervous system to adjust the PEH. Table 2 shows studies that investigated the contribution of this nervous system to the occurrence of PEH. Boone and Jr. Corry⁶² demonstrated that the expression of the gene preproenkephalin (PPK) increases in the CNS after treadmill exercise in SHR, suggesting that increase in PPK synthesis and release in the NTS, CVLM, and RVLM may be involved in regulating PEH. Previous studies on both humans and SHR indicate that endorphin systems (opioid receptor antagonist, naloxone) attenuate PEH, and they trigger the transient depression of blood pressure immediately after running period in the SHR⁶³. In addition, injections of vasopressin V1 receptor antagonist into the lateral cerebral ventricle impedes the manifestation of PEH⁶⁴. This result supports the participation of central mechanisms in the development of PEH, even

though the exact role of each receptor system and the specific site of interaction are still indeterminate.

On the other hand, there is evidence suggesting crucial role of 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 PEH⁶⁵. Correspondingly, Chandler and DiCarlo⁶⁶ observed that sinoaortic denervation, which eliminates arterial baroreflex afferents, participates in development of PEH in SHR. These authors postulated that probably an enhanced inhibitory influence of cardiopulmonary afferents might alter the arterial baroreflex by modulating the response of barosensitive neurons in the NTS to arterial baroreceptor input. These alterations, through resetting of the arterial baroreflex with a reduction in gain, would account for the hypotension, sympathoinhibition, and absence of reflex tachycardia that occurs after a single bout of dynamic exercise in hypertensive rats. Therefore, this data has demonstrated the importance of a functioning baroreflex for occurrence of PEH. Previous investigations have shown reduction of sympathetic nerve activity after exercise⁶⁷, as might be

expected during the lower blood pressure and the baroreflex-mediated regulation of the sympathetic nerve activity must be reset to a lower operating point during PEH.

In the same way, the fundamental role of the RVLM neurons in controlling sympathetic vasomotor tone and blood pressure, the regulatory role of GABA in controlling baseline activity of those neurons and reduced baroreflex function during PEH. Thus, Kajekar et al.⁶⁸ brilliantly suggested evaluating the role of RVLM cardiovascular sympathetic neuronal activity with PEH, as well as the relationship between RVLM sympathetic output with RVLM GABA_A-receptor mechanisms, and with baroreflex sympathetic nerve activity. They concluded that upregulation of GABA signaling at sympathetic cardiovascular RVLM neurons lead to a decreased neuronal output that may contribute to the decrease in sympathetic outflow and hence PEH. Several evidences suggest that muscle afferent fibers release the substance P to activate NK1-R on GABA neurons in the NTS to modify baroreflex function during exercise^{21,69,70}. The data raised the possibility that the unique interaction between the substance P and GABAergic signal transmission systems may contribute to PEH. Based on this information, Chen et al.⁷¹ in an elegant

study confirmed that microinjection of a substance P–NK1-R antagonist in the NTS immediately before exercise attenuates the development of PEH in spontaneously hypertensive rats (SHRs). Since that activation of the NK1-R has been shown to result in the receptor internalization⁷², exercise-induced substance P NK1-R internalization on GABA neurons may provide the unique interaction between the two neurotransmission systems to trigger PEH. Later, Chen et al.⁷³ proposed testing the hypothesis of how a single bout of dynamic exercise decreases the GABA inhibitory synaptic inputs in the NTS baroreceptor second-order neurons via substance P NK1-R internalization on GABA neurons in SHRs, and evidence that a decrease in blood pressure induced by a single bout of exercise in hypertension is mediated in part by downregulation of NK1-R on GABA neurons synapsing on NTS second-order baroreceptor neurons. They concluded that a single bout of dynamic exercise decreases the GABA inhibitory synaptic inputs in the NTS baroreceptor second-order neurons via substance P NK1-R internalization on GABA neurons, and suggest that exercise-induced NK1-R downregulation could provide a potential target for lowering blood pressure in hypertensive subjects.

Table 2. Experimental studies and neural mechanisms associated with PEH.

Authors	Group	Methods (Exercise protocol)	Results	Conclusion
Boone and Jr. Corry ⁶²	Exercise group* Sham-exercise group* *SHR	SHR were randomized to exercise (1) and Sham-exercise (2) groups. Exercise protocol: (1) 40 min of treadmill running at 30 m/min, 10% grade; (2) 40 min of rest on the treadmill.	At 30 min post-exercise preproenkephalin mRNA levels in the NTS, CVLM and RVLM were increased (P < 0.01).	Increases in preproenkephalin synthesis and release in the NTS, CVLM, and RVLM may be involved in regulating PEH.
Collins, Rodenbaugh and DiCarlo ⁶⁴	SHR group	Exercise protocol: All animals were submitted to treadmill exercise (40 min) and sham exercise (40 min sitting on the treadmill). AP was recorded before and after a single bout of dynamic exercise with the central administration of vehicle or the selective AVP V1-receptor antagonist d(CH3)5Tyr(Me)-AVP (AVP-X).	AP decreased below preexercise values (PV) with central administration of vehicle (P < 0.05). After exercise with central administration of AVP-X, AP not significantly different from PV (P > 0.05). AVP-X at rest did not alter AP (P > 0.05).	AVP acting in the central nervous system mediates PEH.
Collins and DiCarlo ⁶⁵	Exercise group* *SHR	Exercise protocol: a single bout of dynamic treadmill exercise (9-12.0 m/min, 10-18% grade for 30-40 min). There were three experimental conditions: control, cardiac efferent blockade*, and combined cardiac efferent and afferent blockade*. *procainamide	MAP significantly decreased in the control and cardiac efferent blockade conditions after exercise. After blocked of cardiac afferents the PEH to mild dynamic exercise was significantly attenuated.	Blockade of cardiac afferents eliminated PEH in the SHR, while blocking the cardiac efferent alone has no effect.
Chandler and DiCarlo ⁶⁶	Intact group* SAD group* *SHR	Exercise protocol: a single bout of dynamic treadmill at 12 m/min, 10% grade for 40 min. Twenty minutes after exercise: cardiac autonomic blockade* and evaluation of PEH. *b1-Adrenergic and muscarinic-cholinergic receptor blocking agents.	After exercise MAP significantly decreased in the intact SHR. But wasn't reduced in the SAD.	SAD prevented the post-exercise reduction in both arterial pressure and cardiac sympathetic tonus. Arterial baroreflex is required for PEH.
Chen et al. ⁷³	Exercise group* Sham-exercise group* *SHR	Exercise protocol: SHR were randomized to: (1) a single bout of exercise on the motor driven treadmill at 15–16m/min and 10° for 40min; or (2) to a sham-exercise group (Sham), placed on the treadmill for 40min with no exercise.	Occurs reduction of the frequency but not of the amplitude of GABA spontaneous IPSCs (sIPSCs); Endogenous substance P influence on sIPSC frequency, and sIPSC frequency response to exogenous application of substance P.	PEH is mediated in part by a downregulation of NK1-R on GABA neurons synapsing onto NTS second-order baroreceptor neurons.

Authors	Group	Methods (Exercise protocol)	Results	Conclusion
Chen et al. ⁷¹	SHR group	Exercise protocol: treadmill at 15 m/min, 10°, for 40 min. AP was taken during and after (2 h) exercise. The vehicle and substance P (NK-1) receptor antagonist injections were made randomly.	The antagonist, in a dose that blocked substance P significantly attenuated the PEH ($P < 0.05$). Vehicle microinjection had no effect.	PEH is mediated, at least in part, by a substance P (NK-1) receptor mechanism in the NTS.
Kajekar et al. ⁶⁸	Exercise group* Sham-exercise group* *SHR	Exercise protocol: treadmill at 15 m/min, 10° for 40 min. Randomly assigned to a (1) single bout of exercise; or to a sham-exercise group placed on the treadmill for 40 min with no exercise. MAP was measured every 10 min during 40 min of exercise or sham exercise and over the next 10 h after exercise or sham exercise	PEH lasted 10 h in SHR. Extracellular Resting RVLM neuronal activity was lower and was increased largely by GABAA-receptor antagonism in PEH versus Sham PEH ($P < 0.05$). Baroreflex control of RVLM neuronal activity operated with a reduced gain ($P < 0.05$).	Upregulation of aspects of GABA signaling at sympathetic cardiovascular RVLM neurons lead to a decreased neuronal output that may contribute to the decrease in sympathetic outflow and hence PEH.
Kulics, Collins and DiCarlo ⁶⁷	Exercise group* *SHR	Exercise protocol: treadmill exercise (9–12 m/min, 10% grade for 40 min). Protocol 1: CO and TPR were determined before, during, and after exercise. Protocol 2: LSNA was recorded before and after exercise.	Associated with the PEH there was a reduction in TPR and an elevation in CO ($P < 0.05$, all comparisons). The reductions in arterial pressure and TPR were associated with a decrease in LSNA ($P < 0.05$)	PEH is mediated by reductions in TPR and SNA

Abbreviations: AP, arterial pressure; PEH, post-exercise hypotension; NTS, nucleus tractus solitarius; CVLM, caudal ventrolateral medulla; RVLM, rostral ventrolateral medulla; MAP, mean arterial pressure; min, minutes; SHR, spontaneously hypertensive rats; WKY, Wistar Kyoto; SAD, sinoaortic-denervated; CO, cardiac output; TPR, total peripheral resistance; LSNA, lumbar sympathetic nervous activity; AVP, arginine vasopressin.

Considerations

The paraventricular nucleus of the hypothalamus (PVN) and the rostral ventrolateral medulla (RVLM) promotes tonic effect on the control of sympathetic vasomotor tone that triggers blood pressure responses. Thus, there are evidences on baroreflex system and central mechanisms related to PEH. The main central mechanisms are (1) interaction between substance P and the GABAergic system in the NTS that contributes to PEH, and (2) baroreceptor neurons disinhibited in the NTS increases RVLM inhibition, via activation of the GABAergic neurons in the CVLM, reduces PEH. We concluded that the nervous system has an important contribution to reduce postexercise blood pressure. In addition, the baroreflex system is important to adjust PEH, as well as nucleus tractus solitarius and RVLM involvement is fundamental to its occurrence.

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