The exercise pressor reflex in hypertension

Masaki Mizuno1,2*, Jere H. Mitchell2 and Scott A. Smith1,2

1 Department of Health Care Sciences, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9174, USA
2 Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9174, USA

Received: August 31, 2016 / Accepted: September 20, 2016

Abstract The cardiovascular response to physical exercise is abnormally exaggerated in hypertension. Since such responses potentially increase the risk for adverse cardiovascular events, it is clinically important to elucidate the cause of this cardiovascular hyper-excitability in this disease. Even if blood pressure is normal at rest, individuals displaying a heightened blood pressure response to exercise are more likely to develop future hypertension. Therefore, early detection of this abnormal circulatory response to physical activity could lead to the early treatment as well as prevention of hypertension. Much evidence suggests that the abnormal exercise pressor reflex (EPR; a reflex originating in exercising skeletal muscle) significantly contributes to the generation of the enhanced circulatory responses in this disease. In addition, it has been demonstrated that the EPR dysfunction is mediated by both mechanically-sensitive fibers associated with the muscle mechanoreflex and chemically-sensitive fibers associated with the muscle metaboreflex. This review focuses on the underlying mechanisms for this over-active EPR function in hypertension. Specifically, updates on our current understanding of the EPR in this disease as well as experimental models used to examine this reflex are presented.

Keywords: blood pressure, heart rate, sympathetic nerve activity, exercise, hypertension

Introduction

The number of adults with hypertension is expected to increase by about 60% world-wide in the next 10 years3). Moreover, hypertension is already one of the most common health problems in the world. The cardiovascular response to physical exercise is abnormally exaggerated in hypertensive patients and characterized by augmented increases in arterial blood pressure, heart rate, and sympathetic nerve activity (SNA)2-10). Since such responses have been shown to be associated with elevated risks for cardiac events such as myocardial ischemia, myocardial infarction, cardiac arrest and/or stroke during and after physical activity, elucidating the cause of this cardiovascular hyper-excitability is clinically as well as physiologically important11-14). The aberrant circulatory response also limits the safety of exercise prescription as a non-pharmacological treatment for hypertension, although habitual exercise is a viable non-pharmacological treatment with demonstrated potential for lowering blood pressure and improving overall cardiovascular health15-17). Moreover, it has been demonstrated that normotensive individuals displaying a heightened blood pressure response to physical activity are more likely to develop future hypertension and are at a greater risk for cardiovascular death18). This suggests that early detection of the abnormal circulatory responses to physical activity could lead to the early treatment and prevention of hypertension in these individuals. Hence, a better understanding of the pathophysiology generating the abnormal cardiovascular response to exercise in hypertensive as well as normotensive individuals would help facilitate this endeavor.

Abnormal exercise pressor reflex in hypertension

Exercise pressor reflex. The sympathetic nervous system is activated during exercise. This exercise-induced sympatho-excitation elevates cardiac contractility and rate, augments venous return and evokes vasoconstriction in the visceral organs and non-active muscle. These cardiovascular adjustments play a critical role in meeting the metabolic demands of exercising muscle19). Afferent signals from working skeletal muscle are one of the important sources of neural input to the cardiovascular centers in the medulla oblongata during exercise and contribute significantly to the regulation of sympathetic outflow as well as the cardiovascular system during physical activity20-23). These contraction-induced signals, which comprise the exercise pressor reflex (EPR), are generated by stimulation of group III (predominantly mechanically-sensitive A-δ fibers associated with the muscle mechanoreflex) and IV (primarily chemically-sensitive C fibers associated with the muscle metaboreflex) skeletal muscle afferents22,24-26).

*Correspondence: masaki.mizuno@utsouthwestern.edu
Exercise pressor reflex in rodent models. Animal models are widely used to examine the function of the EPR, mechanoreflex and/or metaboreflex. Involuntary hindlimb muscle contraction induced via electrical stimulation of the spinal nerve roots is used to examine the respiratory and cardiovascular response to stimulation of the EPR. In cats, electrical stimulation of the L4-L6 ventral roots produces a hindlimb muscle contraction that excites group III and IV afferent sensory neurons that elicit sympathetically-mediated increases in blood pressure and heart rate. As the dorsal roots remain intact, the afferent impulses are able to be transmitted to the brainstem in this model. However, using similar methods in anaesthetized rats, activation of the EPR has been shown to elicit an increase, a decrease, or no change in blood pressure and heart rate. In 2001, our research group clearly demonstrated that anesthesia suppresses the pressor and tachycardic responses to stimulation of the EPR. In an attempt to eliminate this suppression and or reduce these variable responses, we successfully developed a reliable rat model for the study of the EPR by performing pre-collicular decerebration prior to EPR activation. Following decerebration, and after the discontinuation of anesthesia, muscle contraction via ventral root stimulation consistently and reproducibly elicits significant increases in both blood pressure and heart rate.

During exercise, the autonomic nervous system is regulated by integrating neural input from not only the EPR but also central command, a neural drive originating in higher brain centers. The decerebration procedure removes the areas of the cerebral cortex from which central command signals arise, allowing isolation of EPR function. As a result, central command is unlikely to contribute to the sympathetic and pressor responses elucidated in this experimental set-up. The baroreflex is likewise known to contribute to autonomic regulation during exercise. Barodenervation procedures can be readily performed in this rat model further isolating EPR function. The latter is an important point as baroreflex sensitivity is attenuated in hypertension. As a result, it is possible that the exaggerated EPR function demonstrated in hypertensive animals is due to a decrease in the buffering capacity of the baroreflex. However, we have already validated that baroreflex impairment in hypertensive animals contributes minimally to alterations in either EPR or central command function in this disease. Taken together, this rat model is a viable preparation for the study of autonomic function in a variety of disease states. For example, using this experimental setup, Smith et al. provided the first evidence that selective activation of the EPR in spontaneously hypertensive rats (SHR) elicits markedly greater increases in blood pressure and heart rate than in normotensive Wister Kyoto rats (WKY).

Muscle mechanoreflex dysfunction in hypertension. Passive stretching skeletal muscle does not increase muscle metabolism and, therefore, is often used to preferentially engage the stretch-sensitive afferent fibers associated with the muscle mechanoreflex. Using this technique, an additional study by Leal et al. showed that activation of mechanically sensitive fibers by passively stretching hindlimb muscle induced significantly greater increases in blood pressure as well as heart rate in SHR, as compared to WKY, over a wide range of stimulus intensities. This suggests that the skeletal muscle mechanoreflex contributes significantly to EPR overactivity in hypertension. To more completely evaluate the role of the mechanoreflex in this disease, we examined the sympathetic and cardiovascular responses to muscle contraction as well as stretch before and after antagonizing skeletal muscle stretch-sensitive receptors using trivalent lanthanide gadolinium. Gadolinium has been shown to effectively block the activity of mechanically-sensitive afferent fibers in skeletal muscle. Sympathetic and cardiovascular responses to skeletal muscle contraction were significantly attenuated by pharmacologically antagonizing stretch-sensitive skeletal muscle receptors with gadolinium in SHR. Collectively, these findings suggest that the muscle mechanoreflex contributes significantly to the altered EPR-mediated regulation of SNA, blood pressure and heart rate in hypertension. To our best knowledge, there are no studies directly assessing muscle mechanoreflex function in hypertensive humans. However, a recent study by Greaney et al. demonstrated that static handgrip evokes rapid onset exaggerated pressor and sympathetic responses at two distinct intensities (30% and 40 % MVC) within the first 10 s of contraction in older hypertensive adults. These findings suggest that the mechanoreflex may contribute significantly to abnormally high hemodynamic responses to exercise in hypertensive humans as well.

Muscle metaboreflex dysfunction in hypertension. Reports in both humans and animals examining muscle metaboreflex function in hypertension are more controversial. For example, compared with normotensive individuals, adults with moderately elevated systolic blood pressure (138 /79 mmHg) demonstrated greater increases in muscle SNA and blood pressure during handgrip as well as post exercise ischemia. In contrast, other independent studies have demonstrated the SNA response to activation of the metaboreflex is blunted while the blood pressure response is either unchanged or reduced in middle-aged hypertensive patients. In the rat model, to preferentially activate the muscle metaboreflex, we have targeted the transient receptor potential vanilloid 1 (TRPV1) receptor as it has been shown to be primarily localized to group IV afferent fibers and can be activated by several ligands including, but not limited to, protons and the exogenous substance capsaicin. In fact, the TRPV1 receptor has been demonstrated to contribute significantly to EPR activation in normotensive rats. Targeting this receptor, we have provided evidence that the pressor re-
sponse to intra-arterial administration of capsaicin within the hindlimb is consistently augmented in hypertensive compared to normotensive animals. Moreover, the pressor and sympathetic responses to ‘supra-stimulation’ of the muscle metaboreflex during ischemic muscle contraction are likewise markedly augmented in hypertensive compared to normotensive rats. Collectively, these results suggest that the muscle metaboreflex is overactive in hypertension.

To date, it has been extensively demonstrated in a number of animal models of human hypertension that the EPR is overactive in the disease contributing significantly to the exaggerated increases in sympathetic nerve activity and blood pressure that manifest during exercise. We will review the findings from a number of these models to explore the potential mechanisms for the generation of abnormal EPR function in hypertension.

**Renin-angiotensin-aldosterone system (RAAS) induced abnormal EPR function**

**Aldosterone.** Aldosterone is known to contribute to the development of hypertension. Circulating aldosterone penetrates the blood-brain barrier at concentrations parallel to those found in plasma. Aldosterone has been shown to act centrally stimulating the sympathetic nervous system. Earlier studies demonstrated that direct infusion of aldosterone into the cerebral ventricles caused a sustained increase in blood pressure and renal SNA in rats and dogs. As such, aldosterone represents a potential mechanistic candidate for the generation of EPR overactivity. Based on this knowledge, we provided the first evidence that systemic aldosterone administration for 4 weeks (via osmotic minipump) potentiates EPR function. Further, aldosterone induced EPR overactivity is mediated by both functional components of the reflex, the muscle mechanoreflex and metaboreflex.

**Angiotensin.** Angiotensin II, an effector molecule of the RAAS, has also been known to be elevated in hypertension. Koba et al. demonstrated that blood pressure and renal SNA responses to EPR stimulation were significantly exacerbated in rats with hypertension induced by two weeks of subcutaneous infusion of angiotensin II. Further, they indicated that the heightened EPR function was mediated, at least in part, by the mechanical component of the EPR, as the renal SNA response to intermittent (1-to 4-s stimulation to relaxation) bouts of contraction was also exaggerated in this model.

**Dietary induced abnormal EPR function**

**High salt.** High salt intake has also been shown to activate the sympathetic nervous system by increasing sodium concentration in cerebrospinal fluid and neural tissue. We investigated the effects of high salt loading on EPR function and demonstrated that high salt intake alone for 4 weeks significantly augmented the blood pressure, heart rate and SNA responses to activation of the EPR. Similarly, sympathetic and cardiovascular responses to passive stretch as well as capsaicin administration were accentuated by elevated salt intake. These findings are consistent with another report demonstrating that increased dietary salt intake enhances pressor and cardioaccelerator responses to muscle contraction in rats. To further support these findings, it has been previously shown that the pressor responses evoked by direct electrical stimulation of sciatic nerve afferent neurons are increased by high dietary salt intake and decreased by reduced ingestion of dietary salt. Earlier studies demonstrated that increased dietary salt intake enhances sympathetic responsiveness to stimulation of the rostral ventrolateral medulla (RVLM), an established cardiovascular regulatory nuclei within the brainstem. Since salt intake does not alter vascular reactivity to sympathetic stimulation in rats, it is logical to postulate that salt-induced EPR overactivity results from sensitization of the sympathetic nervous system.

**High phosphate.** Since inorganic phosphates are used in the food industry as preservatives, flavor enhancers, and color stabilizers, dietary phosphate (Pi) intake in the United States far exceeds the daily recommendation. High Pi intake is suggested to increase vascular calcification and cardiovascular mortality in patients with chronic kidney disease. More recently a high Pi diet was shown to trigger blood pressure elevation in both normotensive rats and spontaneously hypertensive rats, each with normal kidney function, in the resting condition. Hence, we examined the impact of a high Pi diet on EPR function. We demonstrated that consumption of a high Pi diet augments the cardiovascular and sympathetic responses to activation of the EPR, mechanoreflex and metaboreflex. Importantly, this detrimental effect of a high Pi diet occurs in the absence of renal failure, a disease condition known to be associated with hypertension and augmented EPR function. Altogether, these data provide the first direct evidence that chronic exposure to a high Pi diet induces abnormal EPR function, resembling the phenotype observed in rodent models of non-Pi induced hypertension described above.

**Prenatal insult induced abnormal EPR function**

Evidence suggests that there is an association between small for gestational age infants and the development of hypertension and cardiovascular mortality in later life. For example, in animal models, common prenatal insults such as prenatal administration of glucocorticoids, maternal dietary protein deprivation and uteroplacental insufficiency produces offspring that are small for gestational age and also prenatally programmed to become hyper-
tensive (PPH) in adulthood. Consequently, the models can be used to investigate the mechanisms underlying the development of hypertension in adults born of low birth weight. Renal sympathetic denervation results in the normalization of blood pressure as well as sodium transporter abundance\(^{52,84}\), suggesting a role for the sympathetic nervous system in the development of hypertension with prenatal programming. Based on this background, using a rat model of PPH induced by maternal dietary protein deprivation, we demonstrated that SNA and blood pressure responses to stimulation of the EPR, muscle mechanoreflex or metaboreflex were potentiated in adults compared to control animals\(^{85}\). This suggests that the pathogenesis of EPR dysfunction may play a role in the development of hypertension in adults born small for gestational age. Consistent with these findings, a human study reported a significant increase in basal sympathetic nerve activity in response to the stress of breath holding in those who were born of low birth weight compared to controls\(^{86}\).

**Peripheral mechanisms of exercise pressor reflex dysfunction in hypertension**

**Muscle mechanoreflex.** Angiotensin II is a major contributor to hypertension. NADPH oxidase-derived reactive oxygen species play a critical role in the hypertension induced by angiotensin II\(^{87}\). Koba et al.\(^{62}\) demonstrated that tempol, a membrane-permeable radical scavenger, administered within skeletal muscle, attenuated the blood pressure and renal SNA responses to activation of muscle mechanoreflex in rats with hypertension induced by angiotensin II administration. This group also showed that the generation of muscle superoxide as well as mRNA and protein expression of gp91phox and a NADPH oxidase subunit in skeletal muscle were significantly elevated in the hypertensive rats\(^{62}\). These data suggest that oxidative stress induced by angiotensin II in skeletal muscle contributes to mechanoreflex dysfunction in this form of hypertension. Although it is not a specific mechanism for the abnormal mechanoreflex function in hypertension, recent studies have demonstrated that mechanically-sensitive piezo proteins contribute to the generation of the mechanical component of the EPR in normal rats\(^{48,89}\). As such, these proteins are likewise viable candidates for the pathogenesis of mechanoreflex overactivity in hypertension.

**Muscle metaboreflex.** As discussed previously, the TRPV1 receptor is considered a potential mediator of the muscle metaboreflex response\(^{46,49}\). Supporting this idea, the pressor and sympathetic responses to ischemic muscle contraction both in normotensive and hypertensive animals are attenuated by the administration of the TRPV1 receptor antagonist capsazepine, with the magnitude of the capsazepine-induced reduction being significantly greater in hypertensive compared to normotensive animals\(^{50}\). Furthermore, we have demonstrated that TRPV1 protein expression in dorsal root ganglia is significantly greater in SHR than WKY\(^ {50}\). In addition, we have shown that blockade of the TRPV1 receptor partially corrects metaboreflex overactivity in hypertensive animals supporting a role for this receptor in the manifestation of abnormal reflex function.

In addition to the TRPV1 receptor, it is likely that other skeletal muscle receptors and/or ion channels localized to chemically-sensitive afferent fibers mediate, in part, metaboreflex overactivity in hypertension. For example, acid-sensing ion channels are known to contribute significantly to the muscle metaboreflex in healthy cats\(^ {89-104}\). Recent evidence suggests mechanoreceptors are sensitive piezo proteins contribute to the generation of abnormal EPR functions in hypertension. For example, acid-sensing ion channels are known to contribute significantly to the muscle metaboreflex in healthy cats\(^ {89-104}\). Evidence to support the potential involvement of other receptors in the activation of the metaboreflex has also been reported including the ATP receptors P2X2/3 and P2X3, the bradykinin receptor B2 and the cannabinoid receptor CB1\(^ {50,94}\). Specifically, pharmacological blockade of P2 receptors has been shown to attenuate the exaggerated muscle SNA responses to metaboreflex activation in hypertensive adults\(^ {77}\). Clearly, more research is necessary to definitively determine the skeletal muscle receptors and ligands mediating altered metaboreflex function in this disease.

It is well known that a mismatch between oxygen supply and demand activates the muscle metaboreflex\(^ {50}\). Essential hypertension is associated with a reduction in the microvascular network of skeletal muscle which could increase vascular resistance within muscle during exercise\(^ {95}\). In addition, functional sympatholysis, the normal blunting of sympathetic vasoconstriction in exercising muscle\(^ {26}\), has recently been shown to be impaired in hypertensive animals\(^ {37,97}\) as well as patients\(^ {98}\). These factors could reduce blood flow to exercising muscle and impede the removal of metabolites produced during physical activity. A small population of group III afferent fibers are polymodal in nature, exhibiting a secondary excitatory response to muscle fatigue during skeletal muscle contraction. These neurons appear to be excited by the accumulation of metabolites such as bradykinin, potassium, by-products of arachidonic acid metabolism, and lactic acid\(^ {99,104}\). Recent evidence suggests mechanoreceptors are sensitized by metabolites, specifically during conditions of limited perfusion, thereby enhancing the sympathetic response to mechanoreflex activation\(^ {105,106}\). Therefore, it is logical to suggest that impairments in peripheral blood flow in hypertension could also contribute to the generation of abnormal EPR functions in hypertension via sensitization of the muscle mechanoreflex as well as metaboreflex.

**Central mechanisms of exercise pressor reflex dysfunction in hypertension**

It is plausible that EPR overactivity in hypertension is manifested as a result of changes in the mechanisms by
which afferent signals are processed within the central nervous system. We found that bypassing the skeletal muscle afferent nerve endings by directly stimulating sensory fibers within the sciatic nerve elicited a markedly heightened pressor response in hypertensive animals. This finding opens the possibility that the same level of muscle afferent nerve traffic between normotensive and hypertensive animals is interpreted differently within the central nervous system.

**Nitric oxide.** The nucleus tractus solitarius (NTS) within the medulla oblongata is known to be the most critical for processing EPR sensory information. Evidence suggests that centrally-derived nitric oxide inhibits sympathetic outflow. Using immunohistochemical and western blotting techniques, we showed that the expression of at least one isoform of nitric oxide synthase protein (i.e., neural nitric oxide synthase) is lowered throughout a large portion of the NTS in hypertensive compared to normotensive rats. From such investigation, we further demonstrated that reducing the endogenous production of nitric oxide within the NTS generates overactive muscle mechanoreflex activity in normotensive rats similar to that exhibited in hypertensive animals. Further, in the investigation, blocking the nitric oxide pathway within the NTS augmented the already exaggerated blood pressure response to mechanoreflex activation in hypertensive animals. We also found that increasing nitric oxide production within the NTS partially corrects mechanoreflex overactivity in hypertensive animals. Collectively, the studies support the concept that reductions in nitric oxide within the NTS contribute importantly to the manifestation of abnormal EPR function in hypertension.

**RAAS.** Similar to in the periphery, RAAS in the central nervous system is also a viable candidate for the generation of abnormal EPR function in hypertension. We demonstrated that orally administering the angiotensin converting enzyme (ACE) inhibitor enalapril in prenatally programmed hypertensive rats reduced baseline blood pressure as well as abrogated EPR overactivity. These findings support the contention that RAAS plays a significant role not only in the generation of raised basal blood pressures, but also in the development of the enhanced renal sympathetic and pressor responses to physical exercise. Alternatively, the exposure to prenatal insults during development is accompanied by various changes in neurotransmitter systems. For example, increases in norepinephrine turnover have been observed in the cerebral cortex and locus coeruleus region after fetal stress. These alterations may be responsible for the exaggerated EPR function in prenatally programmed hypertensive rats. Further investigation is needed to clarify the specific mechanisms responsible.

**Epithelial sodium channels.** High sodium intake has been shown to increase the concentration of sodium in cerebral spinal fluid and brain tissue which could evoke central sympathetic activation via epithelial sodium channels. It has been established that epithelial sodium channels are widely expressed in the circumventricular organs. Specifically, it has been suggested that sodium acts on neurons within the organum vasculosum of the lamina terminalis to enhance the responsiveness of sympathetic motor neurons emanating from the RVLM. Continued research in this area is needed to definitively determine whether these pathways underlie high salt intake-induced EPR dysfunction.

**Summary**

The circulatory responses to physical exercise are abnormally exaggerated in hypertension, increasing the risk for the occurrence of deleterious cardiovascular or cerebrovascular events. An increasing number of studies in various animal models of hypertension suggest that EPR dysfunction contributes significantly to this potentiated hemodynamic responsiveness. To date, evidence elucidating both the central and peripheral mechanisms underlying the pathogenesis of abnormal EPR function in this disease is just beginning to emerge. Specifically, studies have demonstrated that EPR overactivity in hypertension is mediated, in part, by the renin-angiotensin-aldosterone system, dietary alterations such as high salt loading and elevated dietary phosphate intake, as well as prenatal insults such as maternal dietary protein deprivation. We recently demonstrated that the abnormally exaggerated EPR function that develops in hypertensive rats is diminished by three months of exercise training via free-wheel running. This suggests that normalization of EPR function may be a mechanism by which exercise training is beneficial for the treatment of this disease. Continuous research will likely prove beneficial to the development of novel therapeutic strategies targeted at reducing the risks associated with physical activity in this disease. This also could help to increase the safety of exercise prescription as a non-pharmacological treatment for hypertension.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this article.

**Acknowledgments**

This research was supported by a grant from the UT Southwestern O’Brien Kidney Research Pilot and Feasibility Program (to M.M.), the National Institutes of Health Heart, Lung and Blood Institute (HL-088422 to S.A.S) and the Lawson & Rogers Lacy Research Fund in Cardiovascular Disease (to J.H.M.).
References


33) Minami N, Yoshikawa T, Kataoka H, Mori N, Nagasaka M,


