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MUSCLE MECHANOREFLEX OVERACTIVITY IN HYPERTENSION: A ROLE FOR CENTRALLY-DERIVED NITRIC OXIDE

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Abstract

The cardiovascular response to exercise is abnormally large in hypertension. Over the past decade, it has become clear that the exercise pressor reflex (a peripheral feed-back mechanism originating in skeletal muscle) contributes significantly to the generation of this hyper-responsiveness. Further, it has been determined that overactivity of the mechanically (muscle mechanoreflex) and chemically (muscle metaboreflex) sensitive components of the exercise pressor reflex underpin its dysfunction. Given the recent attention in the literature, this review focuses upon the aberrant function of the muscle mechanoreflex in this disease. Evidence supporting a role for the mechanoreflex in the pathogenesis of the exaggerated cardiovascular response to physical activity is highlighted. The peripheral and central mechanisms that may be responsible for mechanoreflex overactivity in hypertension are likewise discussed. Particular attention is given to emerging evidence implicating a role for centrally-derived nitric oxide in this process.

Keywords

exercise; blood pressure; heart rate; autonomic nervous system; sympathetic activity; hemodynamics

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1. INTRODUCTION

It is well established that the sympathetically-mediated cardiovascular response to exercise is exaggerated in hypertension. This has been demonstrated on many occasions in both animal models of the disease (Smith *et al.*, 2006; Mizuno *et al.*, 2013) as well as in hypertensive individuals (Aoki *et al.*, 1983; Pickering, 1987; Seguro *et al.*, 1991; Vongpatanasin *et al.*, 2011). Unfortunately, such abnormally large changes in hemodynamics during physical activity increase the risk for adverse cardiovascular or cerebrovascular events during or immediately following a bout of exercise (Hoberg *et al.*, 1990; Mittleman *et al.*, 1993; Mittleman *et al.*, 1996; Kokkinos *et al.*, 2002). This circumstance is regrettable as it limits the safety of exercise prescription as a non-pharmacological treatment for hypertension; a treatment with demonstrated potential for lowering blood pressure and improving overall cardiovascular health (Dengel *et al.*, 1998; Vina *et al.*, 2012; Brook *et al.*, 2013). Clearly, developing strategies that reduce these risks would be greatly beneficial. Determining the mechanisms underlying the potentiated cardiovascular response to exercise in hypertension is an indispensable first step in this strategic development. This review highlights recent advances made towards this end.

2. THE EXERCISE PRESSOR REFLEX IN HYPERTENSION

The autonomic nervous system plays a critical role in regulating the cardiovascular response to physical activity. Three primary mechanisms (Figure 1) produce the autonomic circulatory adjustments requisite for the performance of exercise: i) central command, a feed-forward neural input from higher brain centers putatively emanating from the cerebral cortex (Goodwin *et al.*, 1972); ii) the baroreflex, a negative feed-back system supplying neural input from receptors in the carotid sinuses and aortic arch as well as the heart and lungs (Mancia *et al.*, 1983); and iii) the exercise pressor reflex, a feed-back neural input originating from skeletal muscle (McCloskey *et al.*, 1972). Of these, considerable evidence has accumulated over the last decade demonstrating the exercise pressor reflex contributes appreciably to the abnormally augmented cardiovascular response to exercise in hypertension (Murphy *et al.*, 2011). In this reflex, somatosensory signals from contracting skeletal muscle are transduced to regulatory centers within the brain via thinly-myelinated Group III (A δ) and unmyelinated Group IV (C) afferent neurons (McCloskey *et al.*, 1972; Mitchell *et al.*, 1983). Most Group III afferent neurons are activated abruptly at the onset of muscle contraction with associated receptors (mechanoreceptors) responding primarily to mechanical distortion (i.e. the muscle mechanoreflex) (Kaufman *et al.*, 1984b). The majority of Group IV afferent neurons are stimulated when chemically sensitive receptors (metaboreceptors) are activated by the by-products of skeletal muscle metabolism (i.e. the muscle metaboreflex) (Mense *et al.*, 1983; Kaufman *et al.*, 1984a). Stimulation of these skeletal muscle receptors and their associated afferent neurons during contraction induces hemodynamic changes predominately via increasing sympathetic nerve activity and withdrawing parasympathetic nerve activity (Victor *et al.*, 1989; Matsukawa *et al.*, 1990; Vissing *et al.*, 1991; Matsukawa *et al.*, 1994; Kaufman *et al.*, 1996).

It has been demonstrated that selective activation of the exercise pressor reflex elicits markedly exaggerated increases in blood pressure and heart rate in several rat models of

hypertension (e.g. essential hypertension; prenatally programmed hypertension; angiotensin II induced hypertension) as compared to normotensive controls (Smith *et al.*, 2006; Koba *et al.*, 2013; Mizuno *et al.*, 2013). These enhanced responses are accompanied by augmented increases in renal sympathetic nerve activity and have been shown to be completely abolished by ganglionic and sympathetic blockade with hexamethonium and phentolamine, respectively (Smith *et al.*, 2006; Mizuno *et al.*, 2011a). In patients (Sausen *et al.*, 2009; Delaney *et al.*, 2010; Greaney *et al.*, 2014) and various rat models of hypertension (Leal *et al.*, 2008; Mizuno *et al.*, 2011b; Sala-Mercado *et al.*, 2013), numerous labs have demonstrated that the exercise pressor reflex dysfunction manifest in this disease is driven, in part, by the muscle metaboreflex. These studies are expertly reviewed by Greaney and colleagues in this special issue of *Autonomic Neuroscience: Basic and Clinical*. Equally important, the muscle mechanoreflex has also been implicated in the generation of exercise pressor reflex overactivity in hypertension (Leal *et al.*, 2008). As such, a closer inspection of the muscle mechanoreflex and its function in hypertension is germane.

3. MUSCLE MECHANOREFLEX DYSFUNCTION IN HYPERTENSION

Mechanoreflex dysfunction in hypertension has been demonstrated on several occasions utilizing animal models of the disease. For example, in spontaneously hypertensive rats (a model of human essential hypertension) passively stretching skeletal muscle (a maneuver designed to selectively engage mechanically sensitive afferent neurons) has been reported to elicit markedly potentiated elevations in blood pressure, heart rate, and renal sympathetic nerve activity compared to normotensive Wistar-Kyoto rats (Leal *et al.*, 2008; Mizuno *et al.*, 2011a). This exaggerated responsiveness to mechanoreflex stimulation has been shown to manifest over a wide range of stimulus intensities from low to moderate to maximal. Mechanoreceptor blockade with gadolinium, a trivalent lanthanide, in this model has also been demonstrated to significantly mitigate the augmented cardiovascular response to skeletal muscle contraction in hypertensive animals (Mizuno *et al.*, 2011a). It should be noted that the degree of hypertension in this model can be striking with average mean blood pressures in affected rats greater than 50 mmHg more than their normotensive counterparts. Similar exaggerations in mechanoreflex function have been documented in adult prenatally programmed hypertensive rats (a model of human maternal dietary protein deprivation induced hypertension) (Mizuno *et al.*, 2013; Mizuno *et al.*, 2014b). Compared to spontaneously hypertensive rats, the degree of hypertension in this model is quite modest, primarily affecting systolic blood pressure. Despite this being a milder form of hypertension, the magnitude of the exaggerated cardiovascular response to mechanoreflex activation is similar to that reported in spontaneously hypertensive rats. Collectively, these studies suggest that the muscle mechanoreflex is overactive in multiple forms of hypertension and contributes importantly to exercise pressor reflex dysfunction in this disease. A model of mechanoreflex function in health and after the development of hypertension is presented in Figure 2. Although there has been one published investigation in prehypertensive patients (Choi *et al.*, 2013), no studies examining mechanoreflex function in hypertensive humans have been reported. As such, there remains a clear need to translate the findings derived from animal experimentation to human patients.

4. PERIPHERAL MECHANISMS OF MECHANOREFLEX DYSFUNCTION

To date, the peripheral mechanisms underlying mechanoreflex overactivity in hypertension remain undetermined although several possibilities exist. It is conceivable that the dysfunction results from disease-induced increases in mechanoreceptor expression within skeletal muscle. In support of this concept, early evidence suggests that this may be the case for the closely related metaboreflex where augmentations in the expression of the transient receptor potential vanilloid 1 receptor (a putative metaboreceptor) have been documented in hypertensive animals (Mizuno *et al.*, 2011b). An increase in mechanoreceptor density would be expected to potentiate the activity of the reflex. Equally feasible is the tenet that mechanoreceptors are sensitized in this disease by the presence of elevated levels of exercise-induced metabolites. In both healthy humans (Batman *et al.*, 1994; Middlekauff *et al.*, 2004; Cui *et al.*, 2008) and animals (Stebbins *et al.*, 1986; Rotto *et al.*, 1988; Rotto *et al.*, 1990; Hanna *et al.*, 2003; Li *et al.*, 2003; Hayes *et al.*, 2006; Kindig *et al.*, 2006; Kindig *et al.*, 2007), evidence suggests that metabolites, such as prostaglandin (a by-product of cyclooxygenase-mediated arachidonic acid metabolism) and ATP (working via its purinergic P2X receptor) for example, maintain the ability to sensitize mechanoreceptors and/or mechanically-sensitive afferent neurons. Moreover, it has been established that functional sympatholysis (the local metabolic attenuation of exercise-induced vasoconstriction in working skeletal muscle) is impaired in hypertensive animals (Zhao *et al.*, 2006; Mizuno *et al.*, 2014a) and patients (Vongpatanasin *et al.*, 2011; Price *et al.*, 2013). Impairments in functional sympatholysis effectively reduce blood flow to working skeletal muscle during physical activity allowing accumulation of exercise-induced metabolites. Metabolite accumulation could serve to sensitize local mechanoreceptors. As yet another possibility, increases in oxidative stress within skeletal muscle have been shown to exaggerate exercise pressor reflex activity in hypertensive rats via enhanced superoxide production (Koba *et al.*, 2013). Given that the mechanoreflex is a critical functional component of the exercise pressor reflex, it is logical to suggest that hypertension-induced elevations in skeletal muscle oxidative stress would affect mechanoreflex activity similarly. Table 1 summarizes these potential mechanisms. No matter how plausible, currently each of these possibilities is purely speculative as no studies have been designed, in either animals or humans, to directly examine the peripheral mechanisms underlying mechanoreflex overactivity in hypertension. Clearly, this represents an underserved area of research that warrants additional attention.

5. CENTRAL MECHANISMS OF MECHANOREFLEX DYSFUNCTION

In contrast to the current paucity of evidence supporting a peripheral basis for the generation of mechanoreflex dysfunction in hypertension, several reports have emerged implicating the involvement of the central nervous system. More specifically, studies suggest that the mechanisms by which sensory information from mechanically sensitive afferent neurons is processed within the brain stem are altered in this disease. For example, direct stimulation of skeletal muscle afferent neurons, a maneuver which bypasses skeletal muscle receptors (e.g. mechanoreceptors), has been shown to evoke much larger increases in blood pressure in hypertensive compared to normotensive rats (Mizuno *et al.*, 2011b). Interestingly, this occurs when the intensity of afferent stimulation is equal in both group of animals. Thus it

appears that the same level of afferent nerve activity in normotensive and hypertensive animals is processed but interpreted differently within the central nervous system.

In order to elucidate the mechanisms underlying this altered central nervous system activity, it is important to understand how afferent information from the muscle mechanoreflex is processed. A large portion of Group III mechanically sensitive afferent neurons synapse in the dorsal horn of the spinal cord and subsequently project to the brainstem (Light *et al.*, 1979; Iwamoto *et al.*, 1985; Potts *et al.*, 2002). Several supraspinal regions are known to contribute to cardiovascular regulation during exercise (Loewy, 1990; Waldrop *et al.*, 1996). That being stated, functional, electrophysiological, and neuroanatomical evidence suggests that the site most critical for sensory processing of mechanoreflex input is the nucleus tractus solitarius (NTS) within the medulla oblongata (Kalia *et al.*, 1981; Person, 1989; Toney *et al.*, 1994; Toney *et al.*, 1995). In the NTS, oxidation of L-arginine by nitric oxide synthase (NOS) produces nitric oxide and L-citrulline (Moncada *et al.*, 1993). Experiments suggest that centrally derived nitric oxide, potentially produced from enzymatic reactions involving the endothelial, neuronal and/or inducible isoforms of NOS, inhibits sympathetic outflow from the medullary brainstem (Ruggiero *et al.*, 1996; Lawrence *et al.*, 1998; Alderton *et al.*, 2001; Paton *et al.*, 2001). Under resting conditions, this system contributes to the normal regulation of vasomotor tone (Sander *et al.*, 1999). During exercise, the system modulates reflex mediated changes in sympathetic activity. As evidence, it has been demonstrated in normotensive cats that the sympathetically mediated increases in blood pressure induced by the exercise pressor reflex during muscle contraction are attenuated when the production of nitric oxide is increased within the NTS (Smith *et al.*, 2005). Thus, nitric oxide within the NTS acts to restrain or buffer exercise pressor reflex mediated elevations in blood pressure (Li *et al.*, 2001). Based on this information, it is logical to suggest that centrally-derived nitric oxide performs a similar function in processing mechanoreflex somatosensory input.

Given the regulatory role of nitric oxide within the NTS, it is equally reasonable to suggest that the mechanoreflex-induced exaggerations in cardiovascular hemodynamics in hypertension are mediated through alterations in the central nitric oxide pathway. More specifically, the mechanisms by which nitric oxide modifies input from mechanically sensitive afferent neurons may be altered in hypertension. Decreases in nitric oxide production and availability within the NTS, constitutively and/or during exercise, could elicit both chronic and acute elevations in sympathetic activity, blood pressure, and heart rate by compromising the neuromodulator's restraining/buffering capacity. As proof of concept, a recently published study demonstrated that reducing the endogenous production of nitric oxide within the NTS generates muscle mechanoreflex overactivity in normotensive rats similar to that exhibited in hypertensive animals (Leal *et al.*, 2012). Moreover, the investigation determined that blocking the nitric oxide pathway within the NTS further accentuated the already exaggerated sympathetically mediated cardiovascular response to mechanoreflex activation in hypertensive rats. Complementary experiments established that increasing nitric oxide production within the NTS partially corrects mechanoreflex overactivity in hypertensive animals (Leal *et al.*, 2013). Together, the studies support the concept that reductions in nitric oxide within the NTS contribute importantly to the

manifestation of mechanoreflex dysfunction in hypertension. In addition, they suggest that alterations in the nitric oxide pathway within the NTS contribute to the abnormal processing of mechanoreflex afferent information within the central nervous system in this disease.

In hypertension, reductions in nitric oxide within the NTS could result from deleterious changes in NOS. NOS is essential for the production of nitric oxide within the NTS (Moncada *et al.*, 1993). Therefore, decreases in the expression and/or activity of NOS could translate into reductions in nitric oxide production within the NTS leading to increases in sympathetic outflow at rest and during exercise. Research evidence supports this concept. It has been demonstrated that chronic suppression of NOS within the NTS elicits increases in sympathetic nerve activity, blood pressure, and heart rate in both normotensive rats and cats (Eshima *et al.*, 2000; Wu *et al.*, 2002). Conversely, over-expression of NOS protein within the NTS has been shown to significantly decrease resting blood pressure and heart rate in hypertensive animals (Tai *et al.*, 2004). More recently, using immunohistochemical and western blotting techniques, it has been demonstrated that the expression of at least one isoform of NOS protein (neuronal NOS) is reduced throughout a large portion of the NTS in hypertensive as compared to normotensive rats; although not completely absent in either group of animals (Murphy *et al.*, 2013). Interestingly, it has also been reported that neuronal NOS protein is expressed within or in close proximity to neurons activated by passive muscle stretch; a known mechanoreflex stimulus (Murphy *et al.*, 2013). Other studies have shown that basal NOS activity in the NTS is likewise reduced in hypertensive animals (Pontieri *et al.*, 1998). From such investigation, it appears that the decrease in NOS activity is not due to a lack of substrate but rather may result from an uncoupling of NOS protein or a deficit in NOS expression (Pontieri *et al.*, 1998). Although indirect in nature, collectively these studies support the idea that nitric oxide production is reduced within the NTS in hypertension and may account, in part, for the pathogenesis of mechanoreflex overactivity.

It is likewise well known that reactive oxygen species (e.g. superoxide anion) scavenge nitric oxide both in peripheral tissues and within the central nervous system (Thomas *et al.*, 2001; Paravicini *et al.*, 2006; Hirooka, 2008). Hypertension-induced increases in the production of reactive oxygen species within the NTS could, therefore, diminish nitric oxide availability. The primary source of reactive oxygen species in the brain is nicotinamide-adenine dinucleotide phosphate (NAD(P)H) oxidase (Babior, 2004; Infanger *et al.*, 2006). NAD(P)H oxidase catalyzes the manufacture of superoxide from oxygen. Angiotensin II is known to enhance the activity of NAD(P)H oxidase and, as such, maintains the ability to increase superoxide production within the central nervous system (Zimmerman *et al.*, 2002; Gao *et al.*, 2004). Importantly, all the substrates and enzymes necessary for angiotensin II production and activity (e.g. angiotensin II type 1 receptors) have been identified in brain stem nuclei important to cardiovascular control (Sakai *et al.*, 2005). Therefore, an additional candidate for decreasing nitric oxide availability within the NTS in hypertension is the generation of superoxide via an angiotensin II/NAD(P)H oxidase mechanism. Reductions in nitric oxide availability within the NTS via this mechanism could potentially mediate the elevations in sympathetic activity, blood pressure, and heart rate characteristic of mechanoreflex overactivity. In support of this concept, the density of angiotensin II type 1 receptors is significantly higher in the NTS of hypertensive as compared to normotensive

rats (Song *et al.*, 1994). In addition, studies have demonstrated that the level of reactive oxygen species is augmented in autonomic nuclei important to cardiovascular regulation within the brain stem of hypertensive animals (Kishi *et al.*, 2004). Experiments have further shown that bilateral microinjection of superoxide dismutase mimetics (the enzyme responsible for the breakdown of superoxide) within regulatory brain stem nuclei decreases both resting blood pressure and sympathetic nerve activity in hypertensive animals (Kishi *et al.*, 2004; Tai *et al.*, 2005). More specific to the mechanoreflex, preliminary studies have demonstrated that reducing the activity of endogenously produced superoxide with tempol (a superoxide dismutase mimetic) within the NTS partially corrects the abnormally exaggerated cardiovascular response to passive muscle stretch in hypertensive rats (Hawkins *et al.*, 2009). A schematic depicting the central factors underlying mechanoreflex overactivity in hypertension is presented in Figure 3.

6. SUMMARY

The sympathetically-mediated hemodynamic response to exercise is abnormally exaggerated in hypertension increasing the risk for occurrence of deleterious cardiovascular or cerebrovascular events. Accumulating evidence in multiple animal models of human hypertension suggests the skeletal muscle mechanoreflex contributes significantly to this potentiated hemodynamic responsiveness. At present, very little evidence exists indicating a peripheral mechanism underlies the pathogenesis of mechanoreflex dysfunction in this disease. Conversely, recent data implicates a mechanism of central origin as a likely culprit. Specifically, studies have demonstrated that the nitric oxide pathway within the NTS (the primary center for initial processing of mechanoreflex somatosensory input within the brain stem) is abnormal in hypertension. The data suggest that decreases in the expression/activity of NOS, independent from or in conjunction with increases in the production of reactive oxygen species, reduce the availability of nitric oxide within the NTS. Given that nitric oxide normally acts to restrain or buffer muscle reflex activity, a decrease in the availability of this neuromodulator may underlie the mechanoreflex overactivity manifest in this disease. Although this initial evidence increases our understanding of the derivation of mechanoreflex dysfunction in hypertension, there is a clear need for additional experimentation; particularly in human patients. Continued research in this area may identify novel treatments that, when implemented, reduce the risks associated with exercise in this disease. This could enhance the safety of exercise prescription as a non-pharmacological treatment for hypertension.

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HIGHLIGHTS

- The cardiovascular response to exercise is exaggerated in hypertension
- Skeletal muscle mechanoreflex overactivity mediates this hyper-responsiveness
- Reflex overactivity occurs due to alterations in brainstem nitroxidergic pathways
- Alterations include decreased NOS expression and increased oxidative stress
- Treatment could enhance the safety of exercise prescription in hypertension

Figure 1.

Simplified illustration of the neural inputs regulating autonomic activity during exercise. Central command (putatively originating in the cerebral cortex) and the skeletal muscle exercise pressor reflex (EPR) are actively engaged during physical activity. Each provide input to cardiovascular (CV) centers within the brainstem that primarily induce increases in sympathetic nerve activity (SNA) and decreases in parasympathetic nerve activity (PSNA) during exercise. With regard to the EPR, each functional component of the reflex (i.e. the mechanoreflex and metaboreflex) contributes importantly to this autonomic regulation. In addition, the tonically active carotid, aortic and cardiopulmonary baroreflexes (BARO) modulate the autonomic response evoked by central command and EPR activation. Integration of these inputs mediates the autonomic cardiovascular adjustments required to meet the metabolic demands of physical activity.

Figure 2. Schematic depiction of muscle mechanoreflex activity in health (A) and after the development of hypertension (B). Normally, stimulation of skeletal muscle mechanoreceptors during exercise activates mechanically-sensitive Group III afferent neurons. Signals transduced by these sensory fibers are processed within cardiovascular (CV) centers in the brainstem evoking increases in sympathetic nerve activity (SNA) which mediate appropriate elevations in blood pressure (BP) and heart rate (HR). In hypertension, mechanoreflex activity is accentuated, potentially at several points along its reflex pathway, leading to markedly exaggerated increases in SNA and cardiovascular hemodynamics. These abnormally large sympathetically-mediated circulatory responses to physical activity may increase the risk for an adverse cardiovascular or cerebrovascular event during or immediately following a bout of exercise.

Figure 3.

Schematic illustration of central factors leading to enhanced mechanoreflex mediated increases in sympathetic nerve activity (SNA) in hypertension. Normally, activation of the muscle mechanoreflex elicits increases in SNA. The mechanoreflex likewise induces calcium (Ca^{2+}) entry into the nucleus tractus solitarius (NTS) increasing NO production via neuronal nitric oxide synthase (nNOS). NO production within the NTS serves to buffer/reduce mechanoreflex induced increases in SNA. In this manner, the mechanoreflex finely modulates SNA output to the level requisite for the intensity of exercise being performed. Given this function, factors that reduce NO production/availability within the NTS potentially facilitate mechanoreflex-induced SNA overactivity. In hypertension, reports suggest that NO production within the NTS is compromised via reductions in NOS activity/expression. In addition, reactive oxygen species, such as superoxide ($\text{O}_2^{\cdot -}$), inactivate NO forming peroxynitrite (ONOO^-). The production of superoxide is dependent on NAD(P)H oxidase. Evidence suggests that NAD(P)H oxidase activity is increased in hypertension leading to enhanced superoxide production. This elevated NAD(P)H oxidase activity may be driven by angiotensin II as angiotensin II type 1 receptor (AT1R) expression is enhanced within the NTS of hypertensive rats. The increased generation of superoxide via an angiotensin-II/NAD(P)H oxidase mechanism potentially reduces the NO available for biological activity within the NTS leading to exaggerated increases in SNA. In agreement,

reducing superoxide availability within the NTS by administering tempol (a superoxide dismutase mimetic) mitigates, in part, the exaggerated cardiovascular response to mechanoreflex activation in hypertensive rats.

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Table 1

Potential peripheral mechanisms of mechanoreflex overactivity in hypertension

Mechanism	Potential Effect	Functional Result
Increased expression/density of skeletal muscle mechanoreceptors	Enhanced responsiveness to receptor activation during muscle contraction	Exaggerated mechanoreflex activity
Muscle metabolite accumulation (possibly due to impaired sympatholysis)	Sensitization of skeletal muscle mechanoreceptors / Group III afferent neurons	Exaggerated mechanoreflex activity
Increased skeletal muscle oxidative stress/ enhanced superoxide production	Enhanced stimulation of skeletal muscle mechanoreceptors / Group III afferent neurons during muscle contraction	Exaggerated mechanoreflex activity