Autonomic Neuroscience: Basic and Clinical 188 (2015) 58–63

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Muscle mechanoreflex overactivity in hypertension: A role for centrally-derived nitric oxide

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ARTICLE INFO

Article history:
Received 13 June 2014
Received in revised form 10 December 2014
Accepted 24 December 2014

Keywords:
Exercise
Blood pressure
Heart rate
Autonomic nervous system
Sympathetic activity
Hemodynamics

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.

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 (Mizuno et al., 2013; Smith et al., 2006) 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; Kokkinos et al., 2002; Mittleman and Siscovick, 1996; Mittleman et al., 1993). 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 (Brook et al., 2013; Dengel et al., 1998; Vina et al., 2012). 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 (Fig. 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 and Mark, 1983); and iii) the exercise pressor reflex, a feed-back neural input originating from skeletal muscle (McCloskey and Mitchell, 1972). Of these, considerable evidence has accumulated over the last decade demonstrating that 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 (Aδ) and unmyelinated Group IV (C) afferent neurons (McCloskey and Mitchell, 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

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http://dx.doi.org/10.1016/j.autneu.2014.12.004
1566-0702/

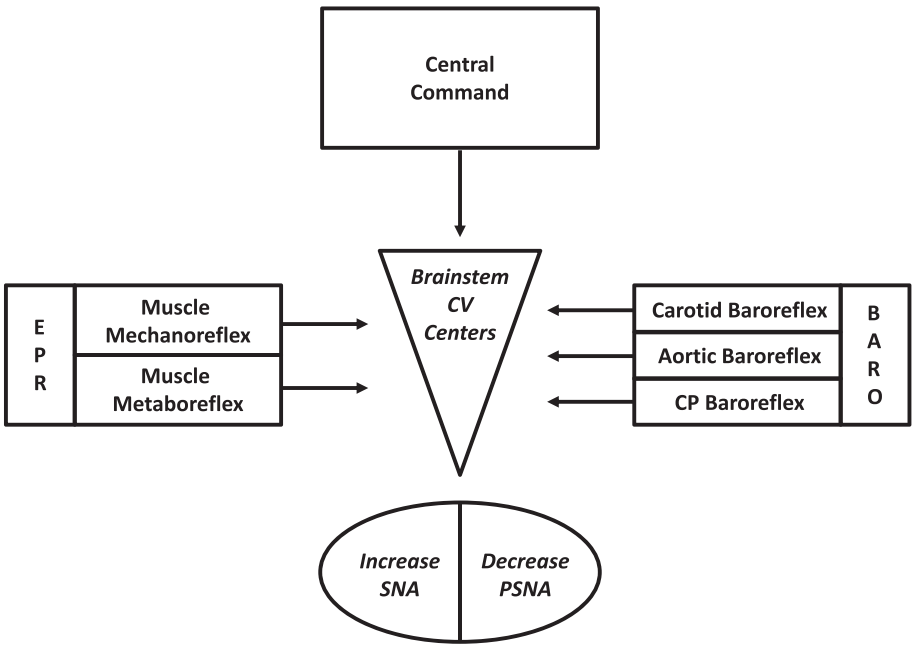

Fig. 1. Simplified illustration of the neural inputs regulating autonomic activity during exercise. Central command (putatively originating in the cerebral cortex) and the skeletal muscle exercise pressor reflex (EPR) are actively engaged during physical activity. Each provides input to cardiovascular (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.

afferent neurons are stimulated when chemically sensitive receptors (metaboreceptors) are activated by the by-products of skeletal muscle metabolism (i.e. the muscle metaboreflex) (Kaufman et al., 1984a; Mense and Stahnke, 1983). 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 (Kaufman and Forster, 1996; Matsukawa et al., 1990, 1994; Victor et al., 1989; Vissing et al., 1991).

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 (Koba et al., 2013; Mizuno et al., 2013; Smith et al., 2006). 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 (Mizuno et al., 2011a; Smith et al., 2006). In patients (Delaney et al., 2010; Greaney et al., 2014; Sausen et al., 2009) 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 et al. 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 mm Hg 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, 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 Fig. 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