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Review

# Exaggerated increases in blood pressure during isometric muscle contraction in hypertension: Role for purinergic receptors

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ABSTRACT

Physical activity is a cornerstone therapy for the primary prevention and treatment of hypertension, which is becoming increasingly prevalent in modern societies. During exercise, heart rate and blood pressure (BP) increase in order to acutely meet the metabolic demands of the working skeletal muscle. In hypertensive adults, isometric exercise-induced increases in BP are excessive, potentially increasing the risk of an acute cardiovascular event during or after physical activity. Recently, the skeletal muscle metaboreflex has emerged as a significant contributor to the development of aberrant cardiovascular control during isometric exercise in this clinical population. Our laboratory has conducted a series of studies characterizing the skeletal muscle metaboreflex in hypertensive humans. We and others have demonstrated that hypertension is characterized by greater increases in muscle sympathetic nerve activity and BP during selective activation of the metaboreflex during post-exercise muscle ischemia compared to the increases noted in healthy age-matched normotensive adults, suggesting that the skeletal muscle metaboreflex is exaggerated in human hypertension. The focus of this review is the skeletal muscle metaboreflex (i.e., the metabolic component of the exercise pressor reflex) in hypertension, with particular emphasis on the potential role of purinergic receptors in mediating the exaggerated responses to muscle metaboreflex activation.



**Contents**



## 1. Introduction

Hypertension is a growing public health burden, affecting ~78 million adults in the US and over 1 billion adults worldwide. Habitual physical activity is a cornerstone therapy for the primary prevention and treatment of hypertension. Indeed, a recent meta-analysis indicates that exercise training – endurance, dynamic resistance, and isometric resistance – significantly reduced blood pressure in hypertensive adults (Cornelissen and Smart, 2013). However, in hypertensive adults, the increases in blood pressure (BP) during exercise are exaggerated (Aoki et al., 1983; Hamada et al., 1987; Matthews et al., 1998). Importantly, these exercise-induced increases in BP occur on top of an already chronically elevated BP thereby potentially increasing the risk of an acute cardiovascular or cerebrovascular event during or immediately after physical activity.

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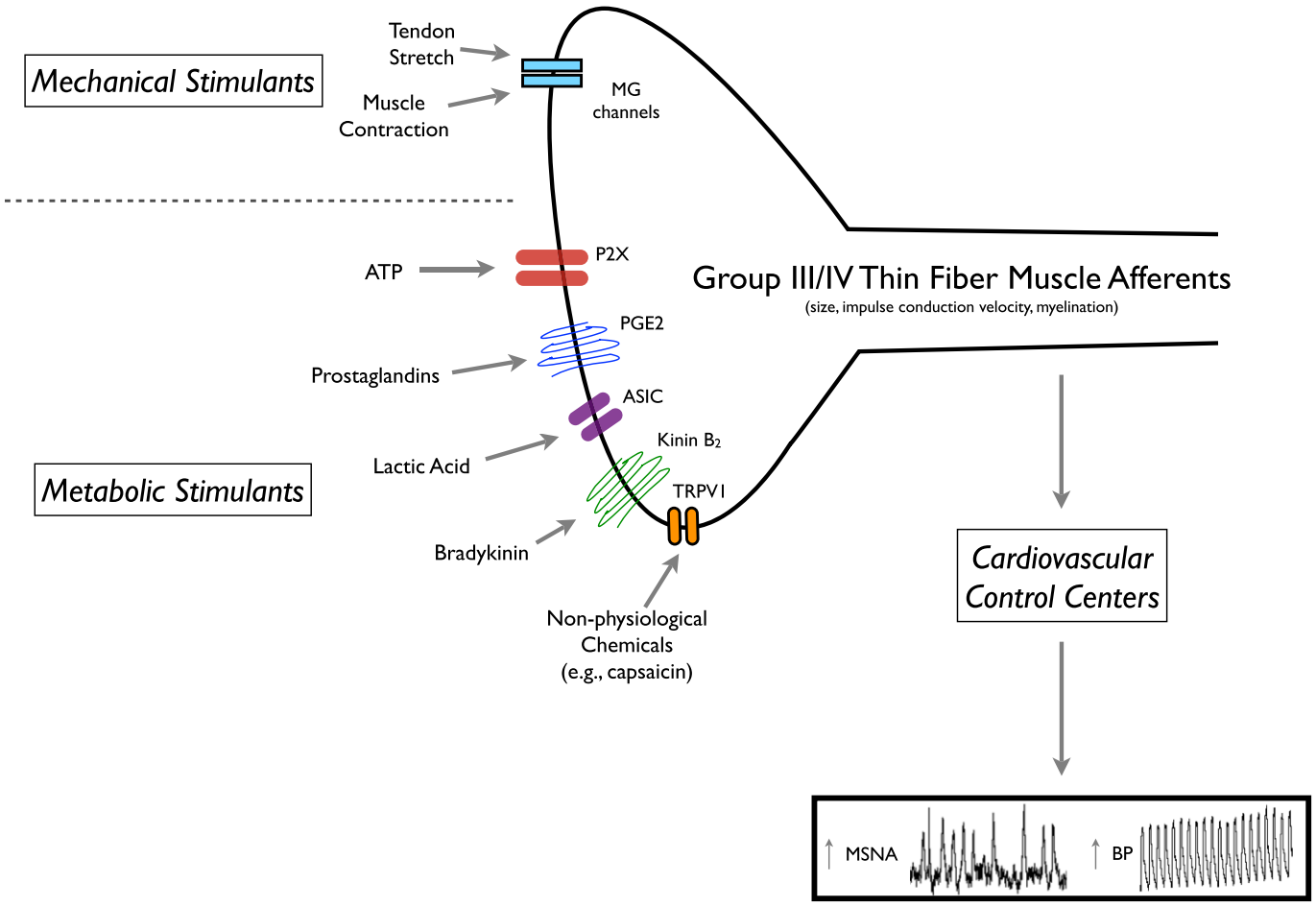


**Fig. 1.** Schematic representation of the exercise pressor reflex (EPR) arc. Several putative stimuli active group III and IV thin fiber muscle afferents during skeletal muscle contraction. Group III fibers are predominately activated by mechanical distortion of their receptive field, likely activating mechanogated channels. Group IV fibers are predominately activated by metabolic by-products of muscle contraction, including potassium, lactic acid, bradykinin, analogues of adenosine triphosphate (ATP), and by-products of arachidonic acid metabolism, in addition to their activation by non-physiological pharmacologic substances. Activation of the muscle mechano- and metaboreceptors transmits impulses, via the spinal cord, to cardiovascular control centers located in the medulla oblongata. Central processing of this afferent input leads primarily to increases in sympathetic nerve activity (SNA), resulting in alterations in heart rate, stroke volume, and total peripheral resistance, subsequently increasing blood pressure (BP) in an intensity-dependent manner. MSNA, muscle sympathetic nerve activity.

During exercise, BP and heart rate increase in order to acutely meet the metabolic demands of the working skeletal muscle. The neurocirculatory responses to muscle contraction are mediated, in part, by the accumulation of metabolites within skeletal muscle and subsequent activation of the sensory fibers comprising the exercise pressor reflex (EPR). This is especially relevant during isometric exercise, which decreases blood flow to active skeletal muscle, thereby attenuating the removal of metabolites produced during muscle contraction and enhancing the stimulation of metaboreceptors located on afferent sensory neurons (Murphy et al., 2011). The precise substances that activate the skeletal muscle metaboreflex and evoke reflex neurocirculatory responses have recently generated substantial research interest. Several candidate metabolites present in exercising muscle have been identified as capable of eliciting cardiovascular responses to muscle contraction including potassium, lactic acid, bradykinin, by-products of arachidonic acid metabolism, and diprotonated phosphate (Rotto et al., 1989, 1990; Rybicki et al., 1984; Sinoway et al., 1994; Stebbins and Longhurst, 1985). As depicted in Fig. 1, these metabolites activate specific receptors, including acid sensing ion channels (ASICs) and transient receptor potential vanilloid 1 (TRPV1) receptors (Kaufman et al., 1982; Michael and Priestley, 1999; Smith et al., 2005; Sutherland et al., 2001), localized on group III and IV afferent sensory fibers within skeletal muscle.

Importantly, several lines of evidence also indicate that purinergic compounds, specifically ATP, activate the muscle metaboreflex (Hanna et al., 2002; Li et al., 2008). Additionally, purinergic ligand-gated ion channels (P2X receptors) have been localized to dorsal root ganglion cells innervating skeletal muscle (Chen et al., 1995; Cook et al., 1997; Lewis et al., 1995; Liu et al., 2011; Wang et al., 2010; Xing et al., 2013). This review highlights the skeletal muscle metaboreflex (i.e., the metabolic component of the EPR) in hypertension, with particular emphasis on the potential role of purinergic receptors in mediating the exaggerated responses to muscle metaboreflex activation. We have attempted to integrate both animal and human studies in order to provide a comprehensive understanding of the work and ideas in these areas. Due to space constraints, we have cited a number of reviews in an attempt to direct the reader to additional research in this field (Fadel and Raven, 2012; Kaufman, 2012; Kaufman and Hayes, 2002; Mortensen and Saltin, 2014; Murphy et al., 2011; Smith et al., 2006a).

## 2. Metaboreflex in hypertension: evidence from preclinical studies

The metaboreflex has been extensively investigated in an animal model of hypertension, the spontaneously hypertensive rat (SHR). Compared to normotensive Wistar-Kyoto rats (WKY), barodenervated SHRs exhibited exaggerated pressor and tachycardic responses to electrically induced muscle contraction (Smith et al., 2006b). Moreover, these augmented hemodynamic responses to contraction were abolished by both the ganglionic blocking agent hexamethonium and the α-adrenergic blocking agent phentolamine, indicating a potential