Autonomic Neuroscience: Basic and Clinical 188 (2015) 69–73

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

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

Review

The exercise pressor reflex and peripheral artery disease

Audrey J. Stone *, Marc P. Kaufman

Heart and Vascular Institute, Penn State College of Medicine, Hershey, PA 17033, United States

ARTICLE INFO

Article history:
Received 8 July 2014
Received in revised form 17 September 2014
Accepted 13 October 2014

Keywords:
Autonomic control
Muscle afferents
Static contraction
Mean arterial pressure
Claudication

ABSTRACT

The exercise pressor reflex contributes to increases in cardiovascular and ventilatory function during exercise. These reflexive increases are caused by both mechanical stimulation and metabolic stimulation of group III and IV afferents with endings in contracting skeletal muscle. Patients with peripheral artery disease (PAD) have an augmented exercise pressor reflex. Recently, an animal model of PAD was established which allows further investigation of possible mechanisms involved in this augmented reflex. Earlier studies have identified ASIC3 channels, bradykinin receptors, P2X receptors, endoperoxide receptors, and thromboxane receptors as playing a role in evoking the exercise pressor reflex in healthy rats. This review focuses on recent studies using a rat model of PAD in order to determine possible mechanisms contributing to the exaggerated exercise pressor reflex seen in patients with this disease.

Contents

1. Introduction

Exercising is known to increase mean arterial pressure, heart rate, and ventilation in both animals and humans (Alam and Smirk, 1937; Coote et al., 1971; McCloskey and Mitchell, 1972; Shepherd et al., 1981). Two mechanisms are thought to cause these increases, namely central command and the exercise pressor reflex. Central command is a "feed forward" mechanism in which the central neural circuits controlling autonomic, ventilatory, and locomotor function are activated simultaneously (Eldridge et al., 1981, 1985; Krogh and Lindhard, 1913). The exercise pressor reflex is a "feedback" mechanism originating in the contracting skeletal muscle which functions to increase cardiovascular and ventilatory function (Alam and Smirk, 1937; Coote et al., 1971; McCloskey and Mitchell, 1972). This review will focus on the second mechanism, namely the exercise pressor reflex.

The sensory arm of the exercise pressor reflex is comprised of thinly myelinated, group III, and unmyelinated, group IV, afferent fibers (Kaufman et al., 1983; McCloskey and Mitchell, 1972). Group III afferents are predominantly stimulated by mechanical stimuli such as

* Corresponding author at: Heart and Vascular Institute, Penn State College of Medicine, 500 University Dr., Hershey, PA 17033, United States. Tel.: +1 717 531 0003x283998 (Work); fax: +1 717 531 0127.
E-mail address: astone1@hmc.psu.edu (A.J. Stone).

http://dx.doi.org/10.1016/j.autneu.2014.10.014
1566-0702/

tendon stretch, light stroking, and squeezing of the triceps surae muscle (Ellaway et al., 1982; Kaufman et al., 1983; Mense and Stahnke, 1983; Paintal, 1960). Group III afferents are also stimulated by intra-arterial injection of putative metabolic stimuli (Kaufman et al., 1983; Kumazawa and Mizumura, 1977; Mense, 1977; Sinoway et al., 1993). Group III afferents conduct impulses between 2.5–30 m/s in cats and between 1.6–10 m/s in rats. Group III afferents often discharge an explosive burst of impulses at the onset of contraction. Their response to contraction often decreases as the muscles fatigue (Kaufman et al., 1983). Group IV afferents are predominantly stimulated by metabolic stimuli produced by muscle contraction (Kaufman et al., 1983; Kenagy et al., 1997; Mense, 1977; Rotto and Kaufman, 1988). These afferents conduct impulses at less than 2.5 m/s in cats and at less than 1.6 m/s in rats, and unlike group III afferents, they do not discharge vigorously at the onset of contraction. They usually respond with a latency of 5–30 s and continue to discharge as the muscle fatigues (Kaufman et al., 1983; Mense and Stahnke, 1983). Thickly myelinated fibers, group I and II afferents (i.e., muscle spindles and Golgi tendon organs), do not contribute to the exercise pressor reflex (Hodgson and Matthews, 1968; Mitchell et al., 1983).

2. Exercise pressor reflex in PAD patients

Peripheral artery disease (PAD) is a progressive narrowing of arteries predominately supplying the lower extremities and is caused by the accumulation of atherosclerotic plaque on the arterial walls (Falk, 2006). PAD affects 8 to 12 million people in the United States, and those people are at a high risk for myocardial infarction and stroke (Criqui et al., 1992; Hirsch et al., 2001). PAD reduces blood flow to working skeletal muscle and results in an augmented blood pressure response to dynamic exercise that is thought to be caused in part by an exaggerated exercise pressor reflex (Baccelli et al., 1999; Bakke et al., 2007), part of which is thought to be evoked by mechanoreceptors (Muller et al., 2012). Oxidative stress has also been shown to play a role in the exaggerated pressor reflex in PAD. For example, the augmented pressor reflex seen in PAD patients was reduced by 50% after infusing ascorbic acid which is an anti-oxidant (Muller et al., 2012). Likewise, renal vascular resistance was also greater in PAD patients than that in healthy controls; this augmented response was also reduced by ascorbic acid infusion (Drew et al., 2013).

3. Animal model of PAD

In rats, PAD is often simulated by ligating the femoral artery just distal to the inguinal ligament. Although femoral artery ligation induces an abrupt stenosis whereas PAD develops slowly over time, this model produces blood flow patterns closely related to those seen in PAD patients (Waters et al., 2004). Prior et al. (2004) showed in a rat a collateral network of vessels arising from the internal iliac artery and connecting to the distal femoral artery–popliteal artery. Femoral artery ligation allows sufficient blood flow to resting skeletal muscle but not to exercising skeletal muscle. In the femoral artery ligation, model blood flow reserve capacity to the hindlimb is reduced and therefore blood flow is not adequate to meet metabolic demand (Prior et al., 2004; Yang et al., 2000). Tsuchimochi et al (2010a) found that 72 h of femoral artery ligation augmented the exercise pressor reflex in decerebrate rats. Pressor responses to static contraction were compared bilaterally between hindlimbs with a freely perfused femoral artery and either a 72 h ligated femoral artery (chronic occlusion) or a 3 min ligated femoral artery (acute occlusion). The pressor responses evoked from chronically occluded hindlimbs were significantly greater than those evoked from freely perfused hindlimbs. Pressor responses from acutely occluded hindlimbs, however, were not different from their contralateral freely perfused hindlimb (Tsuchimochi et al., 2010a).

4. Mechanisms contributing to exaggerated pressor response

The simulated model of PAD was used in rats to identify alterations in the receptors and channels on group III and IV afferents responding to contraction. Previous studies suggested that ASIC3 channels (McCord et al., 2008a, 2009; Rotto and Kaufman, 1988; Rotto et al., 1989), bradykinin receptors (Mense, 1981; Tallarida et al., 1979), P2X receptors (Hanna and Kaufman, 2003; Kindig et al., 2006, 2007a,b) (Hanna and Kaufman, 2004), endoperoxide receptors (McCord et al., 2008b; Rotto et al., 1990), and thromboxane receptors (Kenagy et al., 1997) played a role in evoking the exercise pressor reflex. The following studies examined these mechanisms in an attempt to find the cause for the exaggerated exercise pressor reflex when blood flow to the working skeletal muscle was not sufficient to meet its metabolic demand.

4.1. ASIC3 channels

ASIC3 channels are found on group III and IV afferents in skeletal muscle and are stimulated by protons and lactic acid (Hoheisel et al., 2004). The exaggerated exercise pressor reflex in rats with ligated femoral arteries is attenuated by blockade of ASIC3 receptors. In contrast, the reflex is not affected by ASIC3 antagonists in rats with freely perfused arteries even though the antagonists were shown to be effective in blocking the pressor response to lactic acid injection into the femoral artery of both freely perfused and ligated rats (Tsuchimochi et al., 2011b). Xing et al (2012) found that femoral artery ligation augmented the responses of ASIC3 channels to lactic acid in DRG neurons innervating the hindlimb muscles (Xing et al., 2012). In addition, femoral artery ligation increased ASIC3 expression in DRG neurons stemming from the hindlimb (Liu et al., 2010) and more specifically in C-fiber afferents (Xing et al., 2012).

4.2. TRPV1 receptor

Femoral artery ligation increased in L4–L6 DRG cells both expression of the TRPV1 receptors and their responses to capsaicin. Intraarterial injection of capsaicin evoked greater pressor and RSNA responses in ligated rats than in sham-operated control rats (Leal et al., 2013a; Tsuchimochi et al., 2010a; Xing et al., 2008). Nerve growth factor (NGF) has been found to increase TRPV1 expression and sensitivity (Anand et al., 2006). Further investigation found that NGF was upregulated in IB4-negative DRG neurons when the femoral artery is ligated for 24 h. The response of these DRG neurons to capsaicin was enhanced following 72 h infusion of NGF in the skeletal muscle of the hindlimb (Xing et al., 2009). These findings suggest that NGF contributes to the augmented pressor response to intraarterial injection of capsaicin in ligated rats. TRPV1 receptors did not, however, play a significant role in evoking the exaggerated pressor response to static contraction in ligated rats (Tsuchimochi et al., 2010a). Specifically, blocking TRPV1 receptors with iodo-resiniferatoxin failed to attenuate the exercise pressor reflex even though this TRPV1 antagonist blocked the pressor response to capsaicin (Tsuchimochi et al., 2010a). This suggests that while TRPV1 receptors are upregulated in DRG neurons of ligated rats, they do not play a role in causing the exaggerated exercise pressor reflex seen in this preparation.

4.3. P2X receptors

Several lines of evidence indicate that ATP contributes to the exercise pressor reflex in healthy rats. For example, injection of ATP or an ATP analog into the femoral artery of cats stimulated group III and IV afferents (Hanna and Kaufman, 2004). In addition, P2X3 expression was greater in DRG neurons from the hindlimb of a rat whose femoral artery was ligated for 24 h and 72 h compared to those from freely perfused hindlimbs (Liu et al., 2011). When α,β methylene ATP was injected into the femoral artery of ligated rats, RSNA and MAP responses were