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The exercise pressor reflex and peripheral artery disease

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Abstract

The exercise pressor reflex contributes to increases in cardiovascular and ventilatory function during exercise. These reflexive increases are caused by both mechanical 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.

Keywords

autonomic control; muscle afferents; static contraction; mean arterial pressure; claudication

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 (Krogh and Lindhard, 1913, Eldridge et al., 1981, Eldridge et al., 1985). 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 (McCloskey and Mitchell, 1972, Kaufman et al.,

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1983). Group III afferents are predominantly stimulated by mechanical stimuli such as tendon stretch, light stroking, and squeezing of the triceps surae muscle (Paintal, 1960, Ellaway et al., 1982, Kaufman et al., 1983, Mense and Stahnke, 1983). Group III afferents are also stimulated by intra-arterial injection of putative metabolic stimuli (Kumazawa and Mizumura, 1977, Mense, 1977, Kaufman et al., 1983, Sinoway et al., 1993). Group III afferents conduct impulses between 2.5-30m/s in cats and between 1.6-10m/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 (Mense, 1977, Kaufman et al., 1983, Rotto and Kaufman, 1988, Kenagy et al., 1997). These afferents conduct impulses at less than 2.5m/s in cats and at less than 1.6m/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 5-30s and continue to discharge as the muscle fatigues (Kaufman et al., 1983, Mense and Stahnke, 1983). Thickly myelinated fibers, groups 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).

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).

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 (Yang et al., 2000, Prior et al., 2004). Tsuchimochi et al (2010a) found that 72hrs 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 72hr ligated femoral artery (chronic occlusion) or a 3min 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).

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 (Rotto and Kaufman, 1988, Rotto et al., 1989, McCord et al., 2008a, McCord et al., 2009), bradykinin receptors (Tallarida et al., 1979, Mense, 1981), P2X receptors (Hanna and Kaufman, 2003, Kindig et al., 2006, Kindig et al., 2007b, a) (Hanna, 2004), endoperoxide receptors (Rotto et al., 1990, McCord et al., 2008b), and thromboxane receptors (Kenagy et al., 1997) played a role in evoking the exercise pressor reflex. The following studies examined these mechanisms in 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.

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).

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 (Xing et al., 2008, Tsuchimochi et al., 2010a, Leal et al., 2013a). 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 24hrs. The response of these DRG neurons to capsaicin was enhanced following 72hr 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.

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 24hrs and 72hrs 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 significantly greater than those in freely perfused rats. The increase in P2X3 receptor expression was believed to be in part due to NGF, whose concentration was greater in ligated rats than in freely perfused rats (Liu et al., 2011). Furthermore femoral artery occlusion primarily augmented P2X3 expression in DRG neurons supplied by C-fiber afferents (Xing et al., 2013). These findings suggest that stimulation of P2X3 and P2X2/3 receptors produce greater currents when the hindlimb arterial blood supply has been ligated, and that this increase in P2X3 expression following ligation is largely observed in C-fibers of DRG neurons. Last, when PPADS was infused into the femoral artery of a 72hr ligated rat, the exercise pressor reflex to static contraction was attenuated. PPADS had no effect on the reflex in the freely perfused rats (Stone et al., 2014).

Bradykinin receptors

Bradykinin production in skeletal muscle is increased with exercise (Stebbins et al., 1990, Scott et al., 2004) and is known to stimulate group IV afferents contributing to the exercise pressor reflex (Stebbins et al., 1990). Bradykinin receptor B2, but not B1, mediates the effect of bradykinin on cardiovascular responses when skeletal muscle afferents are stimulated in anesthetized cats (Pan et al., 1993). Lu et al (2013) found that B2, but not B1, receptors were significantly upregulated in DRG neurons from the ligated leg. HOE-140, a B2 receptor antagonist, attenuated MAP and RSNA responses to stretch in both freely perfused and ligated rats but did so to a greater extent in ligated rats (Lu et al., 2013). In contrast, the B1 blocker, R-715, had no effect on MAP and RSNA responses to stretch in freely perfused or ligated rats. In addition, the responses to contraction by group III afferents were attenuated by HOE-140 (Leal et al., 2013a). The effects of B2 receptor blockade on the exercise pressor reflex in ligated rats remains to be determined.

Prostaglandin receptors

Contraction of skeletal muscle produces prostaglandin E2, which in turn stimulates endoperoxide (EP) 3 and 4 receptors on the endings of group III and IV afferents. Yamauchi et al (2013) found that blocking EP4 receptors by injecting L, 161-982 into the femoral artery of a ligated rat, but not that of a freely perfused rat, attenuated the pressor response to

static contraction. EP3 receptor blockade did not attenuate the response. They also found that protein expression of the EP4 receptor but not the EP3 receptor was upregulated in L5 and L4 DRG neurons from the ligated side compared to the freely perfused side (Yamauchi et al., 2013).

Thromboxane receptors

Thromboxane is also produced during muscle contraction when cyclooxygenase metabolizes arachidonic acid. Blocking thromboxane receptors with Daltroban attenuated the exercise pressor reflex in both freely perfused and ligated rats. Further investigation found that thromboxane B2 concentrations in the interstitial fluid obtained from the triceps surae muscles were not significantly increased during 30s of static contraction compared to baseline levels. Nevertheless, intraarterial injection of a thromboxane A2 mimetic did evoke a larger pressor response in ligated rats than that in freely perfused rats (Leal et al., 2011). While the study does not clarify the role of thromboxane in ligated rats, it does suggest that ligating the femoral artery increased either the affinity or number of thromboxane receptors on group III and IV afferents.

Opioid receptors

Previous studies have found that opioid receptors on both the peripheral (muscle) and central (spinal) endings of group III and IV afferents play a role in attenuating the exaggerated exercise pressor reflex seen in rats with ligated femoral arteries. Peripheral stimulation of the μ-opioid receptor with DAMGO injected into the femoral artery significantly attenuated the exercise pressor reflex in ligated but not in freely perfused rats. The muscle mechanoreflex induced by tendon stretch (Stebbins et al., 1988), however, was not attenuated in either freely perfused or ligated rats (Tsuchimochi et al., 2010b). Likewise, peripheral stimulation of the δ-opioid receptor with DPDPE injected into the femoral artery significantly attenuated the exercise pressor reflex well as the mechanoreflex evoked by tendon stretch in both ligated and freely perfused rats. The attenuating effects of DPDPE on the exercise pressor reflex were prevented by Naltrindole, a δ-opioid receptor antagonist. In addition, the δ-opioid receptor protein in the DRG was significantly increased in ligated rats compared to freely perfused rats (Leal et al., 2013b). Contrary to findings concerning μ and δ receptors, stimulation of peripheral K-opioid receptors did not attenuate the exercise pressor reflex or mechanoreflex in either freely perfused or ligated rats. Stimulation of K-opioid receptors on the central endings of K-opioid receptors did, however, attenuate the exaggerated exercise pressor reflex in ligated rats (Copp et al., 2014).

SOD/KATP channels

The effects of Tempol and Tiron, two mimetics of superoxide dismutase (SOD), on the exercise pressor reflex evoked in freely perfused and ligated rats yielded surprisingly different results. Specifically, Tempol, but not Tiron, attenuated the exercise pressor reflex in ligated rats. Neither SOD mimetic had much effect on the reflex in freely perfused rats. In addition, muscle interstitial concentrations of 8-isoprostaglandin, an index of oxidative stress, were not greater in contracting skeletal muscles of ligated rats than they were in contracting muscles of freely perfused rats (McCord et al., 2011). Considered together, these findings suggest that Tempol attenuated the exercise pressor reflex in ligated rats by a

mechanism that was independent of its ability to scavenge reactive oxygen. Subsequently, evidence was provided that this mechanism may be due to the fact that Tempol opens K-ATP channels (Yamauchi et al., 2012). The impact of oxidative stress on the exaggerated pressor reflex in animal models of PAD needs further investigation. Particular attention needs to be paid to improve measures of superoxide production in exercising muscles.

Sodium channels NaV1.8

Voltage gated sodium channels (NaV) conduct impulses in group III and IV afferents. These channels can be categorized as those that are blocked by relatively low concentrations of tetrodotoxin (TTX), which have been termed TTX-sensitive (TTX-s), and those that are blocked by high concentrations of TTX and have been termed TTX-resistant (TTX-r). TTX-r channels, namely NaV1.8 and 1.9, have been found to play a role in pain transmission and therefore were thought to play a possible role in the exaggerated exercise pressor reflex seen in ligated rats. Tsuchimochi et al (2011) found that when tetrodotoxin was placed on the L3-L6 dorsal roots, pressor and cardioaccelerator responses to static contraction and tendon stretch were reduced in both freely perfused and ligated rats. These responses were not attenuated, however, when a purportedly specific NaV 1.8 antagonist (A-803467) was used (Tsuchimochi et al., 2011a). Although findings suggested that TTX-R channels on dorsal root axons did not play a role in the exaggerated pressor response, an additional study found that even though A-803467, when injected intraarterially, did attenuate the exercise pressor reflex, the attenuation may not have been caused solely by NaV1.8 channel blockade (Stone et al., 2013). Specifically, A-803467 blocked muscle spindle activity even though muscle spindles do not have NaV1.8 channels (Djouhri et al., 2003, Stone et al., 2013). The lack of specific antagonists to TTX-r channels limits our ability to investigate the exact role of TTX-r channels in the exercise pressor reflex.

Conclusion

The exercise pressor response is exaggerated in PAD patients, and the mechanisms behind this augmentation have been studied in a rat model where the femoral artery was ligated for 24-72 hours before the start of the experiment. This model simulates the blood flow patterns to exercising muscles in PAD patients. Recent studies have shown that peripheral ASIC3, P2X, and EP4 receptors contribute to the exaggerated exercise pressor reflex evoked by static contraction of hindlimb muscles. In contrast, these studies could not provide evidence that TRPV1 receptors played much of a role in this exaggerated reflex.

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Highlights

- In humans, the exercise pressor reflex is exaggerated in peripheral artery disease
- In rats, the exercise pressor reflex is exaggerated after the femoral artery is ligated for 72hrs
- In rats, ASIC3, P2X, and EP4 receptors contribute to this exaggerated exercise pressor reflex