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Autonomic responses to exercise: Group III/IV muscle afferents and fatigue☆

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ABSTRACT

Group III and IV muscle afferents originating in exercising limb muscle play a significant role in the development of fatigue during exercise in humans. Feedback from these sensory neurons to the central nervous system (CNS) reflexively increases ventilation and central (cardiac output) and peripheral (limb blood flow) hemodynamic responses during exercise and thereby assures adequate muscle blood flow and O_2 delivery. This response depicts a key factor in minimizing the rate of development of peripheral fatigue and in optimizing aerobic exercise capacity. On the other hand, the central projection of group III/IV muscle afferents impairs performance and limits the exercising human via its diminishing effect on the output from spinal motoneurons which decreases voluntary muscle activation (i.e. facilitates central fatigue). Accumulating evidence from recent animal studies suggests the existence of two subtypes of group III/IV muscle afferents. While one subtype only responds to physiological and innocuous levels of endogenous intramuscular metabolites (lactate, ATP, protons) associated with 'normal', predominantly aerobic exercise, the other subtype only responds to higher and concurrently noxious levels of metabolites present in muscle during ischemic contractions or following, for example, hypertonic saline infusions. This review discusses the mechanisms through which group III/IV muscle afferent feedback mediates both central and peripheral fatigue in exercising humans. We also briefly summarize the accumulating evidence from recent animal and human studies documenting the existence of two subtypes of group III/IV muscle afferents and the relevance of this discovery to the interpretation of previous work and the design of future studies.

1. Introduction

Both whole body (e.g. cycling) and single joint (e.g. isometric/dynamic knee extension) exercise of sufficient duration and intensity reduce the force/power generating capacity of muscles involved in the task. This exercise-induced decrease is determined by a peripheral and a central [i.e. related to the central nervous system (CNS)] component (Allen et al., 2008; Gandevia, 2001). 'Peripheral fatigue' encompasses biochemical changes within the contracting muscle leading to an attenuated force/power response to neural excitation. 'Central fatigue', structurally including the brain and the spinal cord, refers to the decrease in force/power secondary to a reduction in descending motor drive and the efficacy of the afferent pathways which combined result in a decrease in the output from spinal motoneurons and thus voluntary muscle activation. Both components of fatigue have previously been linked to group III and IV muscle afferent feedback.

In order to assure a sufficient link to the original work in the face of a restricted number of references, we would be citing various other review articles.

1.1. Group III/IV muscle afferent feedback and exercise: Some basics

With the onset of exercise, contraction-induced mechanical and chemical stimuli begin to activate molecular receptors located on the terminal end of both thinly myelinated (group III) and unmyelinated (group IV) nerve fibers with their receptive fields within skeletal muscle. The exercise-induced activation of these receptors increases the spontaneous discharge of the thin fiber muscle afferents (Adreani et al., 1997; Kaufman et al., 1983; Light et al., 2008) (Fig. 1) that project via the dorsal horn of the spinal cord (Wilson and Hand, 1997; Wilson et al., 2002) to various spinal and supraspinal sites within the CNS (Brooks et al., 2005; Craig, 1995; Craig, 2003). Although the role of group III/IV muscle afferents in the circulatory regulation during exercise has been recognized nearly 80 years ago (Alam and Smirk, 1937), for review see (Secher and Amann, 2012), their fundamental importance in determining exercise hyperpnea was not unanimously agreed upon until recently [for review see (Dempsey et al., 2014)], and their

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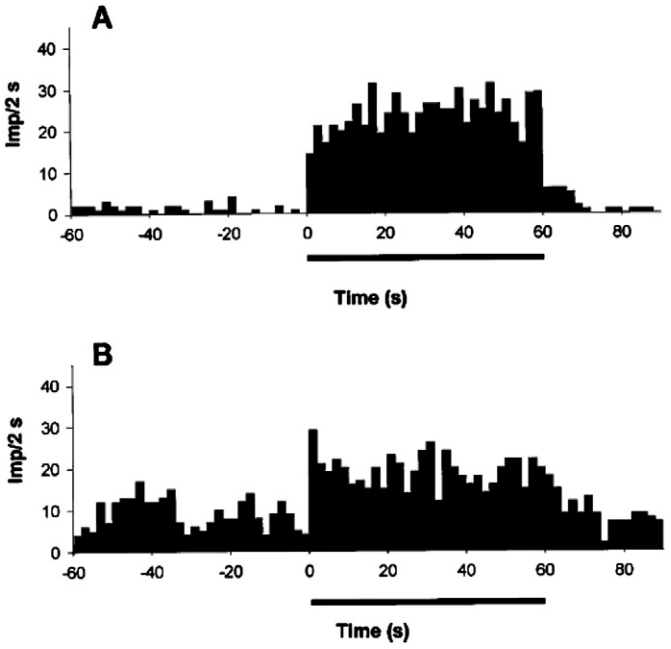

Fig. 1. Discharge frequency [impulses per 2 s; (Imp/2 s)] of group III (panel A) and group IV (panel B) muscle afferents recorded from dorsal root before, during, and after locomotor exercise evoked by electrical stimulation of the mesencephalic locomotor region in decerebrate cats. The horizontal bar denotes the exercise period. Note the immediate increase of both group III and IV locomotor muscle afferent discharge at the onset of exercise and the maintained response until the exercise is terminated. From Adreani et al. (Adreani et al., 1997).

contribution to the development of central fatigue has only been investigated in the last 40 years (Bigland-Ritchie et al., 1986).

With the exception of a few experimental approaches to reduce sensory feedback during and after exercise in humans [e.g. (Gandevia et al., 1990)], the majority of investigations have 'artificially' increased neural discharge of group III/IV muscle afferents to study their role in cardiovascular muscle reflex mechanisms and central fatigue. This approach has included, but was not limited to, intramuscular hypertonic saline (or other metabolite) infusions to stimulate nociceptive muscle afferents (e.g. (Martin et al., 2008) and post exercise circulatory occlusion (PECO) techniques (e.g. (Fisher et al., 2010)) to trap metabolites within a muscle via a blood pressure cuff to maintain/raise neural feedback for as long as the muscle is held ischemic.

2. Group III/IV muscle afferent feedback effects on the development of peripheral fatigue

The role of group III/IV muscle afferents on the development of peripheral fatigue is manifested through their contribution to the cardiovascular, hemodynamic, and ventilatory adjustments occurring during exercise. Increases in these parameters arising with the onset of exercise are, next to central command (Waldrop et al., 1996), largely determined by neural feedback from the working muscle and assure augmented blood flow and O_2 delivery to the working muscle (Asmussen et al., 1943; Coote et al., 1971; Hollander and Bouman, 1975; Kao, 1963; McCloskey and Mitchell, 1972; Tibes, 1977). Both of these variables depict key components in the rate of development of peripheral fatigue during exercise (Barclay, 1986; Fulco et al., 1996; Katayama et al., 2007). Specifically, decreases in blood flow/O_2 delivery exacerbate this rate, whereas increases in blood flow/O_2 delivery attenuate this rate [for review see (Amann and Calbet, 2008)].

In a recent study designed to investigate the role of group III/IV locomotor muscle afferents in the development of peripheral locomotor muscle fatigue, intrathecal fentanyl was used to attenuate sensory feedback from the lower limb during constant-load leg cycling (Amann et al., 2011a). Peripheral fatigue was quantified via the pre- to post-exercise decrease in quadriceps twitch force evoked via supramaximal femoral nerve stimulation. Earlier studies utilizing an identical pharmacological approach to temporarily block group III/IV muscle afferents have documented that exercise in the absence of sensory feedback is characterized by substantial hypoventilation and an attenuated exercise pressor response including decreased central (i.e. cardiac output) and peripheral (leg blood flow) hemodynamic responses during exercise (Amann et al., 2008, 2009, 2010, 2011a, 2011b; Gagnon et al., 2012). Consequently, when constant-load leg cycling is performed in the absence of locomotor muscle afferent feedback, leg blood flow and O_2 delivery are markedly attenuated compared to the same exercise performed with an intact neural feedback mechanism. Given the critical role of blood flow/O_2 delivery in the development of fatigue [see above; (Amann and Calbet, 2008)], the rate of accumulation of peripheral fatigue is up to 60% faster during exercise with impaired vs intact group III/IV muscle afferent feedback (Amann et al., 2011a; Sidhu et al., 2014). Taken together, by facilitating circulatory and ventilatory responses, group III/IV muscle afferent feedback ensures adequate muscle blood flow/O_2 delivery during exercise and thereby prevents premature fatigue at the level of the locomotor muscle. This neural feedback mechanism plays an important role in optimizing fatigue resistance during physical activities in healthy humans.

The arterial baroreflex has been suggested to attenuate the central effects of group III/IV muscle afferents on the exercise pressor response via their interaction in the nucleus tractus solitarii (Kim et al., 2005; Sheriff et al., 1990; Waldrop and Mitchell, 1985). In other words, group III/IV-mediated pressor responses to exercise have been documented to be larger in the absence of the arterial baroreflex. Based on previous experiments in endurance exercising humans showing that attenuated feedback from group III/IV locomotor muscle afferents causes a reduced muscle blood flow/O_2 delivery and accelerated rate of peripheral fatigue (Amann and Secher, 2010, 2011a, 2011b), it could be speculated that arterial baroreflex buffering of group III/IV-mediated muscle reflexes exacerbates the development of peripheral fatigue during exercise. However, Waldrop and Mitchell have shown that the arterial baroreflex modulates the pressor response without changing muscle blood flow during induced muscular contraction in anesthetized cats (Waldrop and Mitchell, 1985). Although unknown in humans, if baroreceptor buffering of muscle afferents does not restrict blood flow to the working muscle, it could be argued that it does not affect the development of peripheral fatigue.

It is important to note that the role of group III/IV muscle afferents in the development of peripheral fatigue might be different in patients with heart failure (Amann et al., 2014) which are characterized by muscle reflex abnormalities (Garry, 2011; Piepoli et al., 2008) with exaggerated afferent feedback as the likely underlying mechanism (Middlekauff and Sinoway, 2007; Notarius et al., 2001; Piepoli and Coats, 2007). Although feedback from these neurons still facilitates central hemodynamics in this population (Amann et al., 2014), it has been documented to account for the excessive hyperventilatory response (Olson et al., 2014) and exaggerated sympathoexcitation (Amann et al., 2014; Notarius et al., 2001) during physical activity in these patients. Recent data demonstrates that when heart failure patients perform single-leg knee-extensor exercise with pharmacologically (lumbar intrathecal fentanyl) blocked group III/IV muscle afferents, sympathetic outflow is attenuated and leg blood flow/O_2 delivery significantly increased compared to control exercise. Importantly, this increase secondary to reduced input from group III/IV muscle afferents causes an attenuated rate of fatigue development in these patients (Amann et al., 2014) (Fig. 2). Therefore, in contrast to healthy individuals in which group III/IV muscle afferent feedback attenuates the rate of peripheral fatigue during exercise (Amann et al., 2011a; Sidhu et al., 2014), the abnormally elevated neural feedback associated with chronic heart failure exacerbates the rate of development of fatigue in these patients (Amann et al., 2014). To our knowledge, there is currently no data