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Significance of Group III and IV muscle afferents for the endurance exercising human

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SUMMARY

1. With the onset of dynamic whole-body exercise, contraction-induced mechanical and biochemical stimuli within locomotor muscle cause an increase in the discharge frequency of thinly myelinated (Group III) and unmyelinated (Group IV) nerve fibres located within the muscle.

2. These thin fibre muscle afferents project to various sites within the central nervous system and thereby substantially influence the exercising human.

3. First, Group III/IV muscle afferents are the afferent arm of cardiovascular and ventilatory reflex responses that are mediated in the nucleus tractus solitarius and the ventrolateral medulla. Therefore, neural feedback from working skeletal muscle is a vital component in providing a high capacity for endurance exercise because muscle perfusion and O₂ delivery determine the fatigability of skeletal muscle.

4. Second, Group III/IV muscle afferents facilitate 'central fatigue' (failure, or unwillingness, of the central nervous system to 'drive' motoneurons) by exerting inhibitory influences on central motor drive during exercise.

5. Thus, Group III/IV muscle afferents play a substantial role in a human's susceptibility to fatigue and capacity for endurance exercise.

Key words: central fatigue, exercise, exercise pressor reflex, human.

INTRODUCTION

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 unmy-

elinated (Group IV) nerve fibres with their receptive fields within skeletal muscle. The exercise-induced activation of these receptors increases the spontaneous discharge of the thin fibre muscle afferents^{1–4} that project via the lumbar dorsal horn of the spinal cord^{5,6} to various sites within the central nervous system (CNS), many of which are currently unknown. The central projection of Group III and IV muscle afferents plays a major role for the exercising human.^{7–9} The purpose of the present brief review is to emphasize the significance of the central effects of these thin fibre muscle afferents on: (i) the cardiovascular and ventilatory responses; and (ii) the regulation of central motor drive during high-intensity endurance exercise.

ROLE OF MUSCLE AFFERENTS IN THE VENTILATORY AND CIRCULATORY RESPONSE TO ENDURANCE EXERCISE

Ventilatory and cardiovascular responses to exercise are primarily regulated by two largely separate systems. The first, a feed-forward mechanism termed 'central command', elicits cardiovascular and ventilatory responses to exercise.¹⁰ The second, a feedback mechanism, reflexly changes ventilation and circulation as a consequence of limb muscle contraction.^{7,11} The focus of the present paper is on the latter.

The first experimental evidence supporting the hypothesis that a reflex response from working muscle may account for a proportion of the cardiovascular¹² and ventilatory¹³ responses to exercise in humans was published approximately 70 years ago. Ever since, numerous animal and human studies have confirmed a key role for muscle afferents in evoking these responses during exercise.^{7,11,14} Specifically, the above mentioned non-nociceptive Group III/IV muscle afferents, the so-called 'ergoreceptors',^{3,15,16} depict the afferent arm of the cardiovascular and ventilatory reflexes,^{7,17–20} which are mediated via neural circuits in the nucleus tractus solitarius and the ventrolateral medulla.²¹

It remains controversial whether afferent feedback from exercising muscle has a considerable contribution to the cardioventilatory response during whole-body endurance exercise or whether the functional significance of this input is limited to conditions of muscle ischaemia, as produced in sustained isometric contractions with compromised blood flow.²² That is, it remains uncertain whether continuous muscle afferent feedback is necessary for adequate ventilatory and circulatory responses during normal rhythmic

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endurance exercise or whether these responses are primarily determined by central command¹⁰ and muscle afferents only depict a temporary error signal²³ to the brain stem reporting an acute mismatch between blood and/or oxygen supply and demand.¹⁸

Recent human studies using local anaesthetics (lumbar epidural space) to block the central projection of Group III/IV muscle afferents during whole-body endurance exercise (leg cycling) found attenuated, similar or even increased cardiovascular and ventilatory responses when the identical exercise was performed with blocked muscle afferents.^{24–29} Although some of these studies conform to the idea that continuous afferent feedback is necessary for adequate ventilatory and circulatory responses, others are contradictory, leaving the exact role of muscle afferents in the cardioventilatory control during endurance exercise controversial. At least some of these conflicting findings may be explained by the use of local epidural anaesthetics, which attenuate efferent as well as afferent nerve activity. The effects of local anaesthetics on efferent nerves cause a drug-induced ‘muscle weakening’,³⁰ which inevitably requires an increase in central motor drive in order to work at and/or maintain a given external workload. Thus, afferent blockade using local anaesthetics creates a condition of reduced feedback in the face of increased feed-forward and this increase in central command, by itself, augments the cardioventilatory response to exercise, as demonstrated in curarization experi-

ments.^{31–33} Therefore, the results from previous studies using local epidural anaesthetics necessitate careful interpretation because the resultant net effect on ventilatory and circulatory responses during exercise with blocked afferent feedback depends on the degree to which the increase in central motor drive balances the reduced feedback from the working limb muscle.^{28,30}

Two recent studies designed to circumvent the confounding impact of local epidural anaesthetics provide valuable insights into the effects of muscle afferents on the circulatory and ventilatory response to whole-body endurance exercise.^{34,35} By using lumbar intrathecal fentanyl, a selective μ -opioid receptor agonist, we were able to inhibit the central projection of Group III/IV muscle afferents without affecting the muscle’s force-generating capacity and therefore without affecting central motor drive/feed-forward during the exercise. The outcome of these studies clearly shows that when Group III/IV muscle afferents from the lower limbs are blocked during endurance exercise of various intensities, ranging from mild to heavy, circulation (Fig. 1) and pulmonary ventilation (Fig. 2) are substantially compromised. This not only causes arterial hypoxaemia and attenuates both perfusion pressure and blood flow, which eventually reduces O₂ delivery to the working muscles, but also facilitates ventilatory and metabolic acidosis,^{34,35} all of which combine to accelerate the development of peripheral locomotor muscle fatigue during exercise.³⁶ These

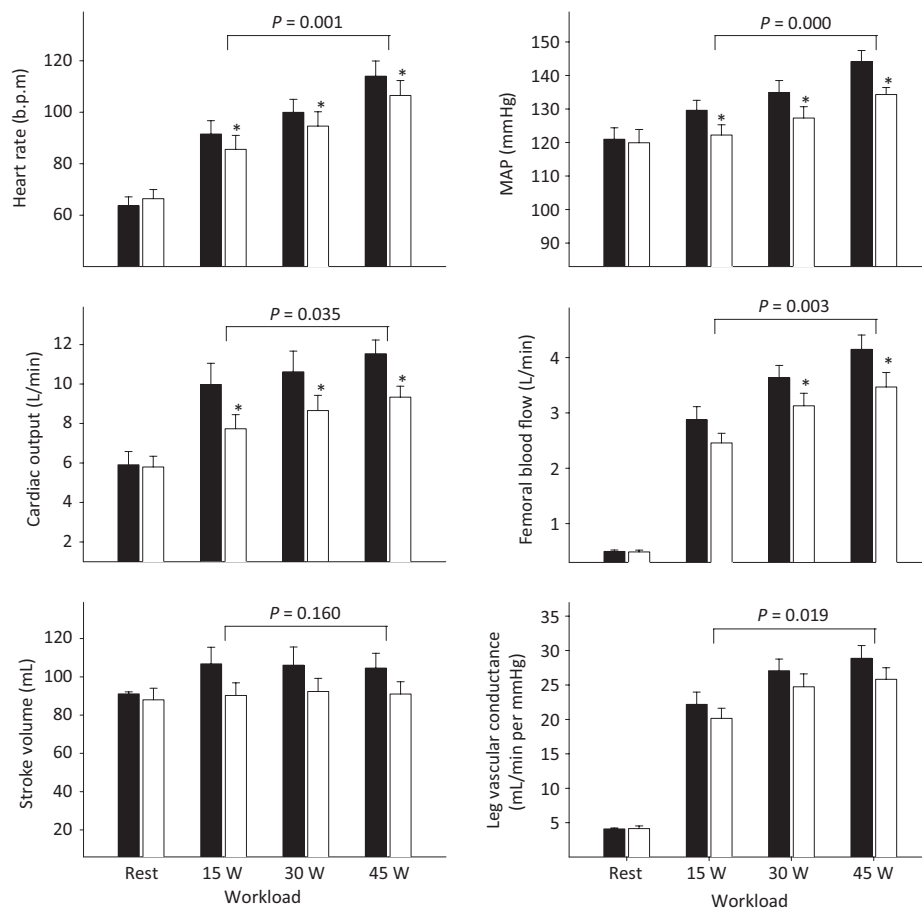


Fig. 1 Circulatory responses at rest and during the final minute of one leg knee extension exercise. The exercise was performed at a low, middle and high exercise intensity (3 min each) with (control; ■) and without (+fentanyl; □) the central projection of lower limb Group III/IV muscle afferents. Data are the mean \pm SD ($n = 9$). The P values indicate the overall main effect of fentanyl. * $P < 0.05$ compared with control. MAP, mean arterial pressure. Modified from Amann *et al.*³⁵

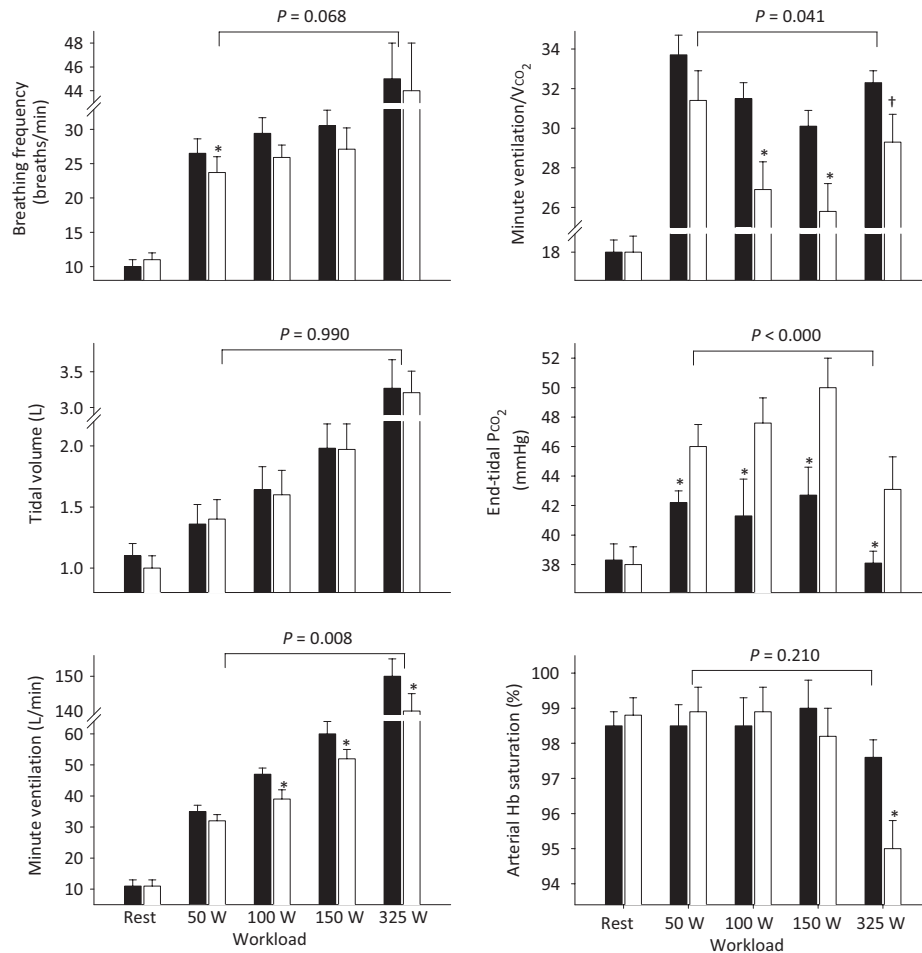


Fig. 2 Ventilatory response and haemoglobin (Hb) saturation at rest and during the final minute of bicycle exercise. The exercise was performed at four different workloads (3 min each) with (control; ■) and without (+fentanyl; □) the central projection of lower limb Group III/IV muscle afferents. Data are the mean \pm SD ($n = 7$). The P values indicate the overall main effect of fentanyl. * $P < 0.05$ compared with control. † $P = 0.08$ (NS) compared with control. Reproduced with permission from Amann *et al.*³⁴

findings suggest that continuous sensory feedback from working skeletal muscle may depict a vital component in providing a high capacity for rhythmic endurance exercise because controlled muscle perfusion and O₂ delivery determine the fatigability of skeletal muscle and thus affect its performance.^{36–38}

EFFECTS OF MUSCLE AFFERENTS ON THE REGULATION OF CENTRAL MOTOR DRIVE DURING EXERCISE

Group III/IV muscle afferents are also known to facilitate central fatigue (i.e. the CNS-mediated reduction in 'driving' motoneurons³⁹) by providing inhibitory feedback to the regulation of central motor drive and voluntary muscle activation during exercise.⁸ This was shown initially during maximal isometric exercise of a single muscle (for a review, see Gandevia⁸). For example, when the discharge rate, and thus the central projection of Group III/IV muscle afferents, is maintained following a 2 min maximal voluntary biceps brachii contraction (via arresting blood flow to and from the arm), central motor drive and voluntary muscle activation remain low and do not recover until circulation is restored and the firing frequency of Group III/IV afferents recovers.⁴⁰

The inhibitory effect of Group III/IV muscle afferents on the regulation of the magnitude of central motor drive is also of critical relevance during high-intensity whole-body endurance exercise.⁹ For example, when subjects performed a 5 km cycling time trial with blocked Group III/IV muscle afferents (via lumbar intrathecal fentanyl), the centrally mediated inhibitory effect of these ergoreceptors was 'attenuated' and central motor drive was less restricted and significantly higher compared with the identical time trial performed with a placebo (Fig. 3).⁴¹ The higher central motor drive resulted in a substantially higher power output during the first half of the race and the CNS 'tolerated' the development of peripheral locomotor muscle fatigue substantially beyond levels observed following the placebo time trial (i.e. performed with intact afferent feedback).⁴¹

Based on sufficient correlative and experimental evidence from us and others over recent years, we propose that the CNS processes neural feedback from locomotor muscle afferents and regulates exercise by adjusting central motor drive in order to confine the development of locomotor muscle fatigue during high-intensity endurance performance (i.e. cycling exercise) to a critical threshold, beyond which the level of associated sensory input would not be tolerated.^{41–45} That is, peripheral locomotor

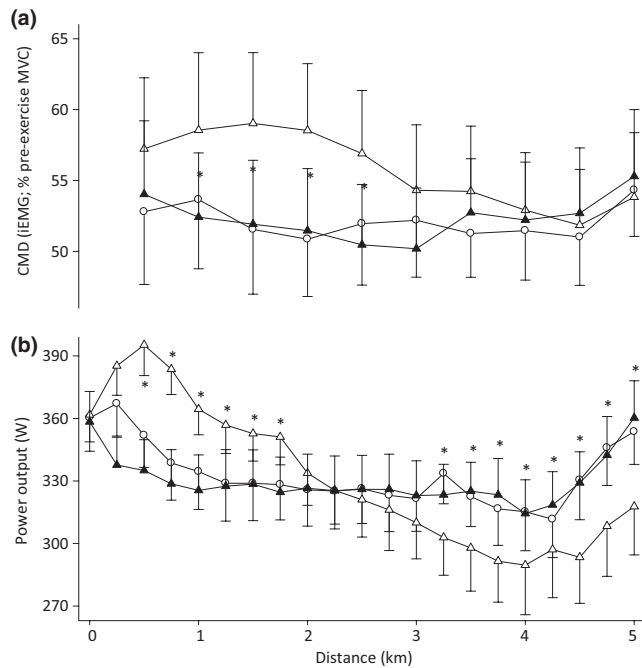


Fig. 3 Effect of lower limb muscle afferent feedback on central motor drive (CMD) and power output. Data were obtained during 5 km cycling time trials performed under control conditions (▲), with a placebo injection (interspinous ligament injection of sterile normal saline, L3–L4; ○) and with intrathecal fentanyl (L3–L4; △). (a) Effects of blocking the central projection of Group III/IV muscle afferents on CMD, estimated via changes in integrated vastus lateralis electromyogram (iEMG), during the race. Mean vastus lateralis iEMG was normalized against the iEMG obtained from pre-exercise quadriceps maximal voluntary contraction (MVC) manoeuvres. Each point represents the mean \pm SD CMD of the preceding 0.5 km section ($n = 9$). (b) Mean power output during the 5 km time trial with and without impaired afferent feedback. Subjects were required to reach an individual target power output before the race was started. * $P < 0.05$ for fentanyl compared with placebo. Reproduced with permission from Amann *et al.*⁴¹

muscle fatigue and associated intramuscular metabolic changes exert, via effects on lower limb muscle afferent feedback, an inhibitory influence on the regulation of central motor drive, thereby limiting the development of peripheral fatigue to an individual threshold. This centrally mediated restriction in the development of peripheral locomotor muscle fatigue may help prevent excessive disturbance of muscle homeostasis and potential harm to the organism.⁴⁶

Although some information is available regarding the brain areas to which nociceptive muscle afferents are projecting,^{47,48} the exact anatomical sites within the CNS that mediate the effects of non-nociceptive Group III/IV muscle afferents on central motor drive are unknown. Neural circuits involved in generating motor cortical output 'upstream' from the motor cortex,^{49,50} as well as the motor cortex itself,⁵¹ have been suggested.

CONCLUSIONS

Group III and IV muscle afferents play a pivotal twofold role for the endurance exercising human. First, continuous afferent feedback from working locomotor muscle is essential for evoking

appropriate ventilatory and circulatory responses during exercise, both of which are critical prerequisites for preventing premature fatigue and accomplishing an optimal performance. Second, Group III/IV muscle afferents provide inhibitory feedback to the CNS, thereby influencing the regulation of central motor drive and limiting the development of peripheral fatigue to a critical threshold, presumably to protect the organism from excessive exhaustion and potentially harm.

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