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Viewpoint

No pain, no gain: somatosensation from skeletal muscle

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The beneficial effects of exercise and exercise training are well recognized and numerous. Not only does participation in regular physical activity improve physical performance (the goal of every athlete), but accumulating evidence suggests it reduces the risk of premature death from all causes. This is likely to be due to its widespread positive effects throughout the human body. For example, training-induced adaptations include, but are not limited to, heightened skeletal muscle stamina and metabolic efficiency, enhanced cardiac function, improved glucose handling, increased insulin sensitivity, reduced body weight and fat deposition, potentiated vascular endothelial function, favourable alterations in parasympathetic–sympathetic balance and decreased resting blood pressure (Vina *et al.* 2012). Furthermore, the benefits of exercise are not only the reward of the healthy, but can also be realized in individuals suffering from disease. Chronic physical training has been shown to evoke improvements in patients with heart failure, hypertension, pulmonary disease, diabetes, arthritis, osteoporosis and cancer, to name a few (Vina *et al.* 2012). As a result, exercise training is commonly used both to promote health and enhance athletic performance and to prevent and treat disease. Given the beneficial effects of regular physical activity in health and disease, understanding the mechanisms that prospectively limit exercise performance is critical. To this end, in this issue of *Experimental Physiology*, Pollak *et al.* (2014) have expertly examined the mechanisms that potentially contribute to the sensations of skeletal muscle fatigue and pain.

Commonly, the sensation of muscle fatigue (i.e. the perception of tired and/or heavy muscles) develops during or immediately after a bout of exercise. The discernment of pain within the muscle is likewise not infrequent, especially during strenuous exercise or physical activity that promotes ischaemic muscle conditions. Each of these sensations can significantly reduce exercise performance and dampen the psychological drive to continue physical activity. As such, the generation of both fatigue and pain can considerably limit exercise tolerance (Amann & Dempsey, 2008). In an attempt to determine the mechanisms underlying the perception of fatigue and pain in humans, Pollak *et al.* (2014) performed a series of chemical infusions (using metabolites known to be produced during exercise) into the abductor pollicis brevis muscle of the thumb. After each infusion, subjects were asked to report and describe any non-pain or pain sensations perceived. Subjects reported no sensations of fatigue or pain when the metabolites (lactate, ATP and protons) were infused individually at concentrations approximating those generated during maximal exercise. Likewise, when the substances were administered concomitantly at concentrations found in resting conditions, no negative sensations were reported. In contrast, combined infusion of the substances at concentrations produced during moderate endurance exercise elicited significant sensations of fatigue. Elevating the combined concentrations to levels found during strenuous physical activity evoked even stronger sensations of fatigue as well as low levels of pain. Increasing the concentrations further to mimic ischaemic exercise caused no additional fatigue, but potentiated the perception of pain. What makes this experimental model interesting and impactful is that the researchers were able to evoke graded sensations of fatigue and pain simply by infusing substances normally produced during exercise independent from the performance of physical activity itself. The research clearly demonstrates, for the first time in humans, that exercise-induced metabolites can elicit sensations of fatigue and pain; not individually, but when working in combination.

The findings of the highlighted study nicely translate previous work in animal models of muscle fatigue and pain to humans. It is well established that nociceptive information is transmitted primarily by group III and IV afferent neurons; neurons known to be activated by a large number of exercise-induced metabolites. In mice, a subset of these metabolites, including lactate, ATP and protons, have been shown to stimulate two different populations of group III and IV neurons innervating skeletal muscle: one responding to metabolite concentrations produced during non-painful muscle contraction (analogous to fatigue) and the other to levels generated during muscle ischaemia (analogous to pain; Light *et al.* 2008). Based on the findings of Pollak *et al.* (2014), these afferents are likely to behave in a similar manner in humans. In addition, work in animals suggests that at least three different receptor types respond to these metabolites, activating associated skeletal muscle afferent neurons when stimulated, namely the acid-sensing ion channel receptors, purinergic receptors and transient receptor potential vanilloid receptors (Light *et al.* 2008). Although direct evidence for the involvement of these receptors in sensing fatigue and pain in humans cannot be derived from the study of Pollak *et al.* (2014), their participation is probable.

Interestingly, group III and IV muscle afferents are also known to contribute significantly to the regulation of the cardiorespiratory response to exercise. Activation of these afferent fibres during physical activity enhances respiration and predominately increases sympathetic output leading to augmentations in heart rate, cardiac contractility and blood pressure (Mitchell *et al.* 1977). Although the infusion-induced sensations of fatigue and pain did not appear to be related to changes in heart rate or respiratory rate, these variables were not measured directly in the highlighted study (Pollak *et al.* 2014). If the infusions did elicit changes in these variables, it would suggest that the same populations of afferents transmitting sensations of fatigue and pain are also responsible for regulating the cardiorespiratory adjustments needed to support physical activity. If the infusions had no effect on haemodynamic or

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pulmonary function, it would suggest that group III and IV afferents can evoke sensations of fatigue and pain independent from changes in cardiorespiratory function. Whether such a dichotomy in function exists in humans requires further investigation.

The highlighted study has demonstrated that, in humans, the perception of fatigue in skeletal muscle is graded and precedes the perception of pain. Speculatively, this suggests that the sensation of fatigue may be a mechanism by which muscle communicates with the brain to serve notice that the limits of exercise tolerance are being approached. The perception of pain, in contrast, may be indicative of impending damage to the muscle if exercise continues. Improvements in muscular performance and endurance are enhanced significantly when the muscle is worked vigorously at regular intervals. Practically speaking, pushing through the sensation of fatigue to the point of pain may maximize the benefits of exercise training and, perhaps, underlies the derivation of the popular colloquial phrase, 'no pain, no gain'. The study by Pollak *et al.* (2014) significantly enhances our understanding of the mechanisms underlying these perceptions in humans.

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