HHS Public Access

Author manuscript

Exp Physiol. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Exp Physiol. 2015 September ; 100(9): 989–990. doi:10.1113/EP085328.

From Petri dish to human: new insights into the mechanisms mediating muscle pain and fatigue, with implications for health and disease

Markus Amann[1,2] and **Alan R. Light**[2,3]

[1]Department of Medicine, University of Utah, Salt Lake City, UT, USA

[2]Department of Anesthesiology, University of Utah, Salt Lake City, UT, USA

[3]Department of Neurobiology and Anatomy, University of Utah, Salt Lake City, UT, USA

With the onset of physical activity, contraction-induced mechanical and metabolic stimuli within working muscle activate molecular receptors located on the terminals of both thinly myelinated (group III) and unmyelinated neurons (group IV). These thin-fibre muscle afferents project, via the dorsal horn of the spinal cord, to spinal and supraspinal sites within the CNS. Over the past 80 years, scientists have recognized the critical involvement of these afferents in the cardiovascular and respiratory responses to exercise, fatigue mediated by the CNS, and musculoskeletal pain (Amann *et al*. 2015). However, despite a century of research, the exact metabolites and intramuscular receptors mediating group III/IV-activated physiological responses and noxious sensations have not been established. Furthermore, the effect of diseases such as heart failure, chronic fatigue syndrome (CFS) or fibromyalgia on the muscle afferent feedback system and the potential role of maladaptations of this system in debilitating symptoms of these diseases are largely unknown.

In the past 15 years, both preclinical and clinical research have greatly increased our understanding of the role that group III/IV afferents play in fatigue and muscle pain. The papers highlighted in this `Connections' article reflect a successful translation of basic animal science (Jankowski *et al*. 2013) into human studies that test the potential physiological relevance of these findings in healthy individuals (Pollak *et al*. 2014) and the subsequent incorporation of that knowledge into clinical research investigating the pathophysiology of disease (Staud *et al*. 2015).

The initial impetus for these research efforts began in Ed McCleskey's laboratory. This group pioneered the concept that combinations of muscle contraction-induced metabolites (ATP, lactate and protons) act synergistically to activate a combination of intramuscular molecular receptors [ASIC3 (Acid Sensing Ion Current 3), P2X5 (Purinergic Receptor P2X, Ligand Gated Ion Channel, 5), and TRPV1 (Transient Receptor Potential Cation Channel, Subfamily V, Member 1] on group III/IV skeletal and heart muscle afferents (e.g. Birdsong *et al*. 2010). This critical work was the basis for our *in vitro* studies using mouse dorsal root

alan.light@hsc.utah.edu

Competing interests None declared.

ganglion neurons to determine a suitable combination of metabolites that mimicked the amounts found in resting, exercising and ischaemic muscle and to evaluate whether group III/IV neurons would respond as predicted. We discovered two different populations of chemosensitive group III/IV muscle afferents. Specifically, one subtype responded to relatively low levels of intramuscular metabolites (lactate, ATP and protons) as seen during `normal' (i.e. freely perfused and aerobic) exercise. In contrast, the other subset responded only to higher concentrations of metabolites present in muscle during ischaemic contractions and musculoskeletal pain, but not to lower concentrations of metabolites associated with normal exercise (Light *et al*. 2008). These afferents were likely the same two subtypes documented in recordings from group III/IV afferents using post-exercise circulatory occlusion vs. freely perfused muscles to increase metabolites (Kaufman *et al*., 1984).

About 5 years later, Jankowski *et al*. (2013) verified and greatly extended these findings. This follow-up work represents a very important advance over our 2008 study. Unlike our experiments that used dissociated cultured mouse dorsal root ganglion neurons (i.e. neuron cell bodies no longer in the muscle), Jankowski *et al*. (2013) used a novel median/ulnar nerve–spinal cord preparation and recorded afferent nerve activity in the intact dorsal root ganglion while applying the same metabolite mixtures directly to the muscle, i.e. the natural site where the metabolites accumulate. These functionally more relevant experiments confirmed the existence of two types of chemoreceptive muscle afferents (i.e. mainly group IV) characterized by different sensitivities to metabolites, distinct neurochemical identities and the involvement of ASIC3, P2X and TRPV1 receptors. The authors identified a subset of chemosensitive afferents that responded to a metabolite mixture found in muscle during normal, non-painful exercise as those traditionally referred to as `metabo- or ergoreceptors'. The afferents that responded to a metabolite mixture found in muscles during ischaemic contractions or musculoskeletal pain were labelled `metabo-nociceptors'. The relevance of these findings for studies focusing on the role of group III/IV muscle afferents in musculoskeletal pain *versus* those focusing on circulation, ventilation and central fatigue during exercise is of great importance. For example, conclusions from studies using postexercise circulatory occlusion techniques, which not only trap metabolites but also increase the intramuscular metabolites further and cause considerable pain, may be limited to the subtype of group III/IV muscle afferents activated by high metabolite concentrations and might not apply to the low-metabolite-responding afferents active during normal aerobic exercise with freely perfused muscles.

At this point, we knew a bit more about the molecular receptors and the combinations of metabolites that activate group III/IV neurons. However, the sensations signalled by each of the two populations of chemosensitive muscle afferents remained elusive. Given that qualitatively different `sensations' cannot be studied in animals, we infused the `metabolite soup' (the combination of ATP, lactate and protons) into the interstitial fluid of a small muscle in the thumb of human subjects (Pollak *et al*. 2014). The infusion of a metabolite mixture similar to concentrations present in resting muscles evoked few sensations. Slightly elevated concentrations, mimicking intramuscular metabolite concentrations present during moderate to intense aerobic exercise, evoked non-painful sensations, the most common of which was fatigue. Interestingly, we found that pain sensations, specifically ache and

burning pain, were evoked by concentrations of the metabolite soup that are present in the muscle interstitial fluid during anaerobic exercise and ischaemia. These findings are in line with previous animal studies (see above) and support the existence of different subtypes of chemosensitive muscle afferents sensing either muscle fatigue (i.e. metaboreceptors) or muscle pain (i.e. metabo-nociceptors). Furthermore, the results from this human study are consistent with the hypothesis that the combination of metabolites that signal fatigue and musculoskeletal pain are protons, ATP and lactate. They are also consistent with molecular detection of these metabolites by group III/IV neurons that have ASIC, P2X and TRPV1 receptors.

Considering these observations, Staud *et al*. (2015) studied the exaggerated fatigue and muscle pain characterizing CFS patients. Using quantitative sensory testing and postexercise circulatory occlusion following exhaustive hand-grip exercise to evoke metabolite-induced sensations of fatigue and pain, these authors investigated whether CFS patients had altered sensitivity of peripheral and/or central neurons. The overall conclusion was that the increased fatigue and pain in CFS patients may, at least in part, be attributable to an increased sensitivity of both sensory afferents in muscle and/or to altered central pain/fatigue processing. Considering earlier findings discussed here, it was proposed that disease-induced alterations of peripheral metaboreceptors, namely ASIC, TRPV1 and P2X, may play a critical role in the pathophysiology of patients with CFS.

Taken together, the three highlighted papers provide significant new insight into the mechanisms determining group III/IV muscle afferent firing and their role in signalling fatigue and musculoskeletal pain. The key findings include the existence of two phenotypically distinct subtypes of group III/IV afferents and the involvement of the molecular receptors ASIC, P2X and TRPV1, which synergistically cause an increase in the discharge frequency of these neurons. These discoveries are highly relevant for our future ability to treat and cure certain human diseases.

This article has many `connections' besides those between the three recently published papers highlighted here. One of the most important is the connection between fatigue, as the inability to contract muscles, and clinical fatigue, as the sensation of fatigue that causes patients to avoid exercise even when it is physically possible, greatly decreasing the quality of life. Another is the connection between fatigue and aching pain. The three publications collectively suggest that the same metabolites that signal fatigue at low concentrations also signal ache at higher concentrations, offering a connection between fatigue and pain.

Acknowledgments

Funding M.A. and A.R.L. are supported by grants from the following: NIH, NHLBI R01 HL116579, VA RR&D, 1I21RX001572, NIH, NHLBI R01HL107529.

References

Amann M, Sidhu SK, Weavil JC, Mangum TS, Venturelli M. Autonomic responses to exercise: group III/IV muscle afferents and fatigue. Auton Neurosci. 2015; 188:19–23. [PubMed: 25458423]

Birdsong WT, Fierro L, Williams FG, Spelta V, Naves LA, Knowles M, Marsh-Haffner J, Adelman JP, Almers W, Elde RP, McCleskey EW. Sensing muscle ischemia: coincident detection of acid and ATP via interplay of two ion channels. Neuron. 2010; 68:739–749. [PubMed: 21092862]

Jankowski MP, Rau KK, Ekmann KM, Anderson CE, Koerber HR. Comprehensive phenotyping of group III and IV muscle afferents in mouse. J Neurophysiol. 2013; 109:2374–2381. [PubMed: 23427306]

Kaufman MP, Rybicki KJ, Waldrop TG, Ordway GA. Effect of ischemia on responses of group III and IV afferents to contraction. J Appl Physiol Respir Environ Exerc Physiol. 1984; 57:644–650. [PubMed: 6092310]

Light AR, Hughen RW, Zhang J, Rainier J, Liu Z, Lee J. Dorsal root ganglion neurons innervating skeletal muscle respond to physiological combinations of protons, ATP, and lactate mediated by ASIC, P2X, and TRPV1. J Neurophysiol. 2008; 100:1184–1201. [PubMed: 18509077]

Pollak KA, Swenson JD, Vanhaitsma TA, Hughen RW, Jo D, Light KC, Schweinhardt P, Amann M, Light AR. Exogenously applied muscle metabolites synergistically evoke sensations of muscle fatigue and pain in human subjects. Exp Physiol. 2014; 99:368–380. [PubMed: 24142455]

Staud R, Mokthech M, Price DD, Robinson ME. Evidence for sensitized fatigue pathways in patients with chronic fatigue syndrome. Pain. 2015; 156:750–759. [PubMed: 25659069]