The acclimatised spinal cord

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A *Perspective* written upon: **JP-RP-2017-274872R1** **‘**UBC-Nepal Expedition: Acclimatization to high-altitude increases spinal motoneurone excitability during fatigue in humans’ by Luca Ruggiero, Alexandra F Yacyshyn, Jane Nettleton, and Chris J McNeil.

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Fatigue is a universal and daily phenomenon that involves a myriad of complex mechanisms ultimately characterised as an exercise-induced decrease in the maximal force produced by a muscle (Gandevia *et al.*, 1996). The investigation of fatigue dates back to the early 19th century with the work from Alessandro Mosso and colleagues, however, today there is still debate among the scientific community about the appropriateness of defining and measuring 'fatigue' for different populations and exercise tasks (Enoka & Duchateau, 2016). A significant amount of the decline in maximal force occurs through processes which exist in the muscle, yet, changes in the performance of any, or all sites from the motor cortex to the muscle fibre, may contribute to fatigue. Thus, the impairment in muscle performance is not necessarily the limiting factor in force production from a fatigued muscle (Gandevia *et al.*, 1996). Over the last 70 years, stimulation techniques have been utilised to enable the measurement of fatigue and subsequently, sites of fatigue have been compartmentalised into those that exist within the muscle and the central nervous system (CNS). More specifically, over the last 20 years, the use of transcranial magnetic stimulation (TMS) has enabled greater investigation into the fatigued CNS and in line with the use of motor nerve stimulation, TMS enables excitability of the brain to muscle pathway to be quantified. As such, this technique has become a popular tool to monitor changes in CNS function in many paradigms within exercise science.

The sites implicated in the fatigue response are augmented when exercise is performed under conditions of environmental stress. The ability to perform exercise, whether it be an isolated limb activity or whole body manoeuvre, deteriorates in line with increasing altitude. At severe levels of altitude (arterial oxy-haemoglobin saturation <75%), the site of fatigue is predominantly located within the CNS and TMS has been used to demonstrate this in a number of investigations. Following a prolonged stay at altitude the level of CNS fatigue is attenuated, along with an associated increase in excitability of the brain to muscle pathway (Goodall *et al.*, 2014). However, one aspect that was not determined in the Goodall *et al.* (2014) investigation, and moreover a parameter that is infrequently studied during the investigation of fatigue, is how the change in spinal excitability contributes to the overall change in excitability of the corticospinal tract. Responsiveness of the motoneurone pool can be studied using cervicomedullary junction stimulation; the size of a resultant evoked potential (CMEP) provides information on excitability of the spinal tract. In this issue of *The Journal of Physiology*, a study has focused on the changes in motoneurone excitability and fatigue that are observed during exercise in acute hypoxia, and following a period of chronic hypoxia (Ruggiero *et al.*, 2017). Confirming previous findings, Ruggiero and colleagues (2017) found that the acute hypoxic environment elicited the greatest amount of fatigue and specifically, this was due in part, to a sub optimal output from the motor cortex. Supraspinal fatigue developed earlier in acute hypoxia (8 mins), compared to normoxia and chronic hypoxia (16 mins). Furthermore, in acute hypoxia and normoxia, there was a fatigue related reduction in motoneurone excitability, however, in chronic hypoxia responsiveness of the motoneurone pool was not depressed and the CMEPs were larger than what was observed in the acute condition (Ruggiero *et al.*, 2017).

The findings from Ruggiero *et al.* (2017) help to explain the results of Goodall *et al.* (2014) who found a two fold increase in corticospinal excitability after a period of chronic hypoxia, however, those authors concluded such a change was due to adaptations in spinal and/or supraspinal sites. It is now clear that the heightened corticospinal excitability observed previously (Goodall *et al.*, 2014), was in part, due to an acclimatised motoneurone pool (Ruggiero *et al.*, 2017). The timing of the measurements made during chronic hypoxia in both of the aforementioned investigations (between 6 and 18 days), correspond with the window for maximal sympathetic norepinephrine concentration following exposure to high altitude (Barnholt *et al.*, 2006). Ruggiero and colleagues (2017) explain that norepinephrine acts as a potent neuromodulator, acting to increase motoneurone excitability. Such an increase seems a logical mechanism for the manipulation of motoneurone responsiveness in chronic hypoxia. Notably, given that output from the motoneurone pool is imperative for muscle contraction, it follows that high altitude adaptation of intrinsic motoneurone properties can explain, in part, the superior exercise performance commonly observed following a period of high altitude acclimatisation.

Ruggiero and colleagues (2017) should be congratulated on the execution of this excellent study which is the first to demonstrate a direct effect of acclimatisation within the spinal cord. From a personal perspective, I know that venturing to altitude in order to undertake such experiment is not without its challenges and complexities. Most investigations reporting the mechanisms of acclimatisation tend to focus upon the cardiovascular and haematological adaptations which are of course of great importance, but it is now clear that widespread changes are apparent throughout the neuromuscular system. As a logical next step, it is worthwhile to investigate the change in intrinsic motoneurone properties of locomotor muscles and understand the potential impact of this on the common improvement in exercise performance observed following acclimatisation. However, most notably for the field of high altitude physiology is that we are beginning to fully understand the integrated adaptation which occurs throughout the human body during acclimatisation.

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