Skeletal muscle ROS and glucose uptake during contraction

G.K. McConell[1] and T.L. Merry,[2] [1]Institute of Sport, Exercise and Active Living and the School of Biomedical and Health Sciences, Victoria University, VIC 8001, Australia and [2]Department of Sport and Exercise Science, University of Auckland, New Zealand.

Exercise stimulates skeletal muscle glucose uptake by increasing GLUT-4 translocation from intracellular vesicles to the cell membrane through a mechanism(s) that differs from insulin stimulation. Although the pathway(s) through which contraction stimulates skeletal muscle glucose uptake is unclear, there is evidence for separate and collective contribution of several signalling intermediates including AMP-activated protein kinase (AMPK), nitric oxide (NO), calcium/calmodulin-dependent kinase (CaMK) and more recently, reactive oxygen species (ROS).

Exposure of isolated skeletal muscle to exogenous ROS increases glucose uptake (Toyoda *et al.*, 2004). In addition, intense contraction of isolated mouse EDL muscle increases ROS production and the antioxidant N-acetylcysteine (NAC) attenuates increases in skeletal muscle glucose uptake (Sandstrom *et al.*, 2006). Although Sandstrom *et al.* presented evidence to suggest that AMPK may play a role in ROS-mediated glucose uptake during contraction, we have recently shown that the increase in glucose uptake during *ex vivo* contraction is attenuated by NAC similarly in wild type and AMPK kinase dead mouse muscle (Merry *et al.*, 2010c). hese results indicated that ROS regulate skeletal muscle glucose uptake during *ex vivo* contraction *via* AMPK-independent mechanisms. Interestingly, we have preliminary evidence suggesting that nitric oxide and ROS may interact during *ex vivo* contractions to regulate skeletal muscle glucose uptake, potentially *via* S-glutathionylation and/or peroxynitrite signalling.

Until recently the role of ROS in the regulation of contraction-stimulated skeletal muscle glucose uptake had only been examined using these isolated muscle models. In the absence of blood flow, such models depend on diffusion gradients for substrate delivery and clearance, and result in non-uniform delivery of oxygen to all muscle fibres. Furthermore, *ex vivo* muscle preparations generally involve supra-maximal highly fatiguing stimulation protocols. Therefore, we investigated the role of ROS signalling in the regulation of skeletal muscle glucose uptake during contraction/exercise in intact preparations by infusing NAC during moderate intensity *in situ* contractions in rats (Merry *et al.*, 2010a) and during exercise in humans (Merry *et al.*, 2010b). Unlike *ex vivo* contraction, we found that NAC did not affect skeletal muscle glucose uptake during contractions *in situ* and exercise *in vivo*. These results provide evidence that under physiological contraction/exercise conditions ROS may not be involved in the regulation of skeletal muscle glucose disposal and that previous results obtained using intense *ex vivo* contractions may not be relevant to normal exercise. However, more studies are required in this emerging area of interest before definitive conclusions can be drawn.

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