Skeletal muscle glucose metabolism in health and metabolic disease

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The ability to manipulate the germ-line of the mouse has led to advances in virtually every area of physiology and disease. Coupled with the use of radioactive tracers, in particular glucose analogs to determine whole-body and tissue specific glucose metabolism, the mouse can be a powerful experimental tool. Nevertheless, the small size of the mouse makes stress-free study difficult in the conscious state. This has been overcome by the implementation of unique methods that have been designed specifically to avoid stress, thus allowing for elucidation of factors that regulate glucose metabolism in the whole organism which, ultimately, is what we aim to know.

We have previously shown that mice expressing a kinase-dead form of AMP-activated protein kinase (AMPK; a key energy sensor within skeletal muscle), causes deleterious effects with regards to skeletal muscle glucose metabolism *in vivo* (Lee-Young *et al*., 2009). This was in part due to impaired delivery of glucose to skeletal muscle, impaired mitochondrial function within skeletal muscle, and a switch in the cellular fate of glucose from glycogen synthesis towards oxidation. We also found that the expression of neuronal nitric oxide synthase (nNOSμ), a downstream target of AMPK, was impaired in kinase-dead AMPK mice. Interestingly, impaired nNOSμ, seen in metabolic disease states such as Type 2 diabetes (Bradley *et al.*, 2007), is associated with all of the glucose metabolism defects seen in kinase-dead AMPK mice (Finocchietto *et al.*, 2008). AMPK can interact with nNOSμ, and given the impairment in glucose metabolism seen with either AMPK or nNOSμ deficiency, we have aimed to determine whether nNOSμ does play a role in the regulation of skeletal muscle glucose metabolism, and whether AMPK is indeed required for the regulation of nNOSμ in skeletal muscle.

We are now focussing on the role of skeletal muscle nNOSμ in the regulation of mitochondrial function and glucose metabolism, showing that defects seen in kinase-dead AMPK mice are at least partly due to alterations in nNOSμ. This leads to the question of whether AMPK does indeed regulate nNOSμ expression in skeletal muscle, thereby providing new ways to increase skeletal muscle nNOSμ expression *in vivo*.

Bradley SJ, Kingwell BA, Canny BJ & McConell GK (2007). Skeletal muscle neuronal nitric oxide synthase micro protein is reduced in people with impaired glucose homeostasis and is not normalized by exercise training. *Metabolism*, **56**, 1405-1411.

Finocchietto P, Barreyro F, Holod S, Peralta J, Franco MC, Mendez C, Converso DP, Estevez A, Carreras MC & Poderoso JJ (2008). Control of muscle mitochondria by insulin entails activation of Akt2-mtNOS pathway: implications for the metabolic syndrome. *PLoS One* **3**, e1749. doi: 10.1371/journal.pone.0001749

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