Protection of muscle membrane excitability during cycling in humans: a role for SGLT3?

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TO THE EDITOR: Intracellular processes are known to be regulated by extracellular glucose concentration, although the precise mechanism/s by which this occurs remains to be established and may vary between tissues. One of the earliest identified “glucose-sensing” mechanisms is the glucose-induced insulin release from pancreatic beta cells (1). Insulin release from pancreatic beta cells appears to be mediated by cellular glucose catabolism and, more specifically, changes in ATP:ADP ratio, leading to inhibition of ATP-sensitive transmembrane K⁺ channels (K_{ATP} channel; Ref. 7), although other mechanisms are not precluded (3, 7).

Glucose-induced changes in membrane potential are known to occur in other tissues that are reliant on glucose metabolism including glucose-sensitive and glucose-responsive neurons (5) and smooth muscle cells (6, 7). For instance, acute high glucose concentration (10–20 mM) has been shown to reduce K_{ATP} currents of the human omental artery (4), a mechanism proposed to operate via the production of superoxide and mediated by the activation of protein kinase C (PKC; Ref. 4). Interestingly, not unlike the pancreatic beta cells, the metabolism of the monosaccharide (D-glucose or fructose) seems critical for the change in membrane potential since L-glucose and other non-metabolizable sugars are without effect (6).

Building on findings in the anaesthetized rat, a recent paper published in the Journal of Applied Physiology revealed that glucose may exert similar action on skeletal muscle membrane excitability during prolonged cycle exercise in humans (8). Prolonged cycling with oral glucose supplementation was associated with higher M-wave amplitude (mV) at 90 min (87%) compared with cycling without glucose supplementation. Importantly, glucose supplementation resulted in a significant elevation of blood glucose concentration (50%) and at fatigue (87%) compared with cycling without glucose supplementation. Interestingly, the observed difference in M-wave amplitude properties between glucose supplemented exercise and non-glucose-supplemented exercise occurred independent of any differences in intramuscular substrates or metabolic responses investigated (8).

While a possible role for the Na⁺/glucose cotransporter, SGLT3, has not previously been reported in these papers, recent characterization of human SGLT3 (hSGLT3) has revealed its function to be analogs to that of a “glucose sensor” (2). Indeed, electrophysiological assays showed that glucose induced a specific phlorizin-sensitive, Na⁺-dependent depolarization of the membrane potential, by up to 50 mV (2). Furthermore, hSGLT3 is expressed in the plasma membrane of human skeletal muscle at the neuromuscular junction and the glucose-induced inward currents demonstrated a linear association with glucose concentration (2). Finally, previous studies have demonstrated a high selectivity of SGLT3 for D-glucose (9) and while the exact intracellular cascade associated with SGLT3 is still being elucidated, the interaction between glucose transporters and PKC are well described. As such, the combined direct and indirect evidence have led previous researchers to suggest a role for SGLTs and specifically hSGLT3 in regulating muscle activity (2).

In summary, the purpose of this letter is to highlight hSGLT3 as a possible candidate for the observed changes in membrane potential of skeletal muscle during periods of glucose-supplemented exercise (8).

REFERENCES