Exercise, nitric oxide and glucose metabolism

G.K. McConell, Institute of Sport, Exercise and Active Living (ISEAL), Victoria University, Footscray Park, VIC 8001, Australia.

The number of people with diabetes in Australia has been described as an epidemic having trebled since 1981. Type 2 diabetes (T2D) accounts for over 85% of people with diabetes. Insulin is released into the blood after a meal and this stimulates insulin sensitive tissues, especially skeletal muscle to take up this glucose. Indeed, skeletal muscle is the major site of glucose disposal in response to insulin. More than 70% of insulin-stimulated whole-body glucose uptake occurs in skeletal muscle, and reduced glucose uptake by muscle is the major contributor to the decrease in whole-body insulin-stimulated glucose uptake in T2D. This reduction in insulin resistance in people with T2D is due to both reductions in insulin signalling within skeletal muscle cells and also due to reduced insulin stimulation of muscle capillary blood flow.

Most people are aware that “exercise is good for diabetes”. It is often assumed that this is because chronic exercise (exercise training) causes weight loss and since around 80% of people with T2D are overweight, this is indeed a great benefit of exercise. However, importantly, exercise training increases skeletal muscle insulin sensitivity, independently of weight loss. It is also underappreciated that each acute bout of exercise also increases insulin sensitivity in both healthy individuals and those with T2D. Therefore, there are both acute and chronic effects of exercise on insulin sensitivity.

The mechanism(s) responsible for this increase in skeletal muscle insulin sensitivity after acute exercise are unclear and do not appear to involve proximal insulin signalling. There is some evidence that nitric oxide (NO) may have insulin sensitising effects and indeed there is evidence that chronic L-arginine supplementation (NOS substrate) and nitrate supplementation (non-enzymatic source of NO) appear to increase insulin sensitivity (Carlstrom *et al.*, 2010; Piatti *et al.*, 2001). In addition, eNOS and nNOS knock out mice are insulin resistant (Shankar *et al.*, 2000). We have shown in many studies that NO plays a critical role in skeletal muscle glucose uptake *during* contraction (Piatti *et al.*, 2001). We showed that NOS inhibition attenuates the normal increase in skeletal muscle glucose uptake during contractions in mice (*ex vivo*) and rats (*ex vivo* and *in situ*) and during exercise in healthy controls and in people with T2D (McConell *et al.*, 2012). These effects were independent of blood flow (McConell *et al.*, 2012). Preliminary evidence indicates that NO is also required for the increase in insulin sensitivity after *ex vivo* contraction of mouse muscle and also after exercise in humans. The isolated muscle studies suggest that these effects may be largely independent of blood flow and therefore involve the muscle *per se*.

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