Skeletal muscle microvascular blood flow and insulin action

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Skeletal muscle is an important site for insulin-mediated glucose disposal in the post-prandial state (Keske *et al.*, 2009). The classical action of insulin to increase muscle glucose uptake involves insulin binding to receptors on myocytes to stimulate the insulin signalling pathway leading to GLUT4 translocation to the cell surface membrane, enhancing glucose uptake. However, an additional role of insulin on muscle glucose uptake is its action to increase muscle blood flow thereby improving insulin and glucose delivery to myocytes. Insulin can increase large blood vessel (*e.g.* total limb blood flow) as well as small blood vessel (*e.g.* microvascular) blood flow (Vincent *et al.*, 2004; Premilovac *et al.*, 2014). However, insulin-mediated glucose uptake is modified by microvascular blood flow and not total limb blood flow (Vincent *et al.*, 2004). This microvascular action of insulin is mediated, at least in part, by nitric oxide synthase (Vincent *et al.*, 2004; Kubota *et al.*, 2011) and accounts for 40-50% of insulin-stimulated glucose disposal in skeletal muscle (Vincent *et al.*, 2004). Skeletal muscle microvascular blood flow is impaired during insulin resistance (Premilovac *et al.*, 2014; Kubota *et al.*, 2011) and type 2 diabetes (Russell *et al.*, 2017). There is a growing body of literature suggesting that impairments in microvascular insulin action have important physiological consequences in the early pathogenesis of insulin resistance and can precede myocyte insulin resistance (Premilovac *et al.*, 2014; Kubota *et al.*, 2011; Bonner *et al.*, 2013). Therefore, interventions targeting the microcirculation in skeletal muscle is a novel approach to improve glucose homeostasis in insulin resistant states (Premilovac *et al.*, 2014; Russell *et al.*, 2017).

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