Integrated control of muscle glucose uptake in health and disease - insights from transgenic mice

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Glucose intolerance and insulin resistance are conditions of growing prevalence that can progress to diabetes and are risk factors for cardiovascular disease. Muscle comprises the bulk of insulin-sensitive tissue and dramatically increases glucose uptake with exercise. Consequently one cannot define the regulation of glucose metabolism without understanding glucose uptake by muscle (MGU). MGU requires glucose delivery from vasculature to muscle, glucose transport into the muscle, and glucose phosphorylation within the muscle. Stimulation of MGU can result from acceleration of one or more of these steps, while impaired glucose uptake can result due to an impediment in one or more of these steps. The capacity of insulin to act on muscle is also an integrated process requiring robust transfer of the hormone from capillaries to myocytes and binding to its cell surface receptor with activation of intracellular signaling proteins. Our laboratory has defined sites of control for MGU and insulin action *in vivo* using transgenic mouse models and pharmacological tools. Genetic overexpression and partial knockout of GLUT4 or hexokinase were used to elucidate sites of control of MGU in lean mice. Membrane transport was shown to be the primary site of control of MGU in sedentary fasted mice, while phosphorylation was demonstrated to be the primary site of control during exercise. Insulin stimulation was so efficient at stimulating glucose transport in lean mice that control of MGU shifted to vascular glucose delivery and phosphorylation. High fat (HF) feeding results in insulin resistance and is associated with expansion of the muscle extracellular matrix (ECM) and impaired vascularity, as well as defects in the muscle itself. The importance of the ECM and muscle vascularity was emphasized by studies that show that administration of sildenafil, relaxin, and hyaluronidase prevented or reversed ECM expansion, increased muscle capillaries, and improved muscle insulin-stimulated MGU in HF fed mice. Deletion of the cell surface integrin $\alpha 2\beta 1$ receptor that binds ECM collagens results in increased capillaries and insulin-stimulated MGU. This suggests that the interaction of this integrin dimer with collagen contributes to the deleterious effect of ECM expansion on insulin resistance. Reciprocally, a primary reduction in capillary number due to muscle-specific VEGF deletion created insulin resistance in lean mice, providing further evidence that muscle insulin resistance is due, at least in part, to extramyocellular events. In summary, studies in conscious mice show that the rate of MGU is defined by the distributed control paradigm, where vascular access to the muscle is a key regulatory element in both health and insulin resistance.