Skeletal muscle fat metabolism and insulin resistance: old targets, new players

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Insulin resistance and type 2 diabetes are frequently accompanied by triglyceride (TG) accumulation in skeletal muscle. However, it is not known whether TG deposition in skeletal muscle causes insulin resistance or whether reducing TG improves insulin sensitivity. We addressed these questions using loss and gain-of-function approaches. Acyl CoA:diacylglycerol acyltransferase 2 (DGAT2), an enzyme that catalyses the final step in TG biosynthesis, was genetically overexpressed in the skeletal muscle of mice by using the muscle creatine kinase promoter. This resulted in enhanced TG deposition in skeletal muscle and was associated with insulin resistance as assessed by whole body insulin and glucose tolerance tests and reduced 2-deoxyglucose uptake in isolated muscle. This occurred independent of changes in other lipid metabolites and serine / threonine kinases known to interfere with insulin signal transduction. We next tested whether increasing TG turnover would prevent fat-induced insulin resistance. To do this we overexpressed the novel triglyceride lipase, adipose triglyceride lipase (ATGL) in skeletal muscle myotubes by retroviral transfection and in rat tibialis anterior by electroporation of an ATGL vector. Anaesthesia was induced with 5% and maintained with 1–2% halothane in oxygen, the surgical site was irrigated with bupivicaine (0.5 mg/100 g) before closure, and 5 mg/kg ketoprofen was administered to provide postoperative analgesia. ATGL overexpression in myotubes increased the oxidation of fatty acids liberated from TG, but resulted in diglyceride and ceramide accumulation. These responses in cells were largely recapitulated in rats overexpressing ATGL. When ATGL protein expression and TG hydrolase activity in obese, insulin resistant rats were restored to levels observed in lean rats, TG content was reduced; however, the insulin resistance induced by the high fat diet persisted as assessed by hyperinsulinemic-euglycemic clamp. Collectively, these studies indicate that TG accumulation can cause insulin resistance and that short-term turnover of TG by ATGL overexpression does not protect against fat-induced insulin resistance.