Manipulating Ketone Metabolism as a Glucose-Lowering Target in Obesity and Type 2 Diabetes

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It is well characterized that perturbations in energy metabolism are present in individuals with obesity-associated type 2 diabetes (T2D). One of the most notable perturbations is the result of metabolic inflexibility in skeletal muscle, which interferes with the transition to increased reliance on carbohydrates (i.e. glucose) as a fuel source following nutrient ingestion. Of interest, we have also observed that the skeletal muscle in obesity/T2D oxidizes more ketones, an endogenous fuel source made by the liver during prolonged fasting/starvation. This was reflected by an increased activity of succinyl CoA:3-ketoacid CoA transferase (SCOT), the rate-limiting enzyme of ketone oxidation. We have demonstrated that genetic deletion of SCOT in skeletal muscle produces a robust glucose-lowering response against experimental obesity/T2D. Furthermore, through in silico modeling we identified the first pharmacological agent that can inhibit SCOT, an older generation anti-psychotic agent belonging to the diphenylbutylpiperidine (DPBP) drug class, pimozide. Intriguingly, treatment with pimozide also produced robust glucose-lowering in experimental obesity/T2D, suggesting that pimozide, and possibly other DPBP agents, may have clinical utility in being repurposed for the treatment of T2D.