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COMMENT ON SATO ET AL.

Improving Type 2 Diabetes Through a Distinct Adrenergic Signaling Pathway Involving mTORC2 That Mediates Glucose Uptake in Skeletal Muscle. Diabetes 2014;63: 4115–4129

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Sato et al. (1) showed that β_2-adrenoreceptor–mediated phosphorylation of mammalian target of rapamycin complex 2 (mTORC2) in skeletal muscles increased GLUT4 translocation to the plasma membrane and thus increased cellular glucose uptake. In diabetes and obesity, an upregulated G-protein–coupled receptor kinase, which inhibits G-protein–coupled receptors, has been reported to contribute to insulin resistance in skeletal muscle (2). In support of this, the current study demonstrated an increased peripheral glucose uptake following β_2-adrenoreceptor activation in diabetic rats and obese mice (1). However, the statement that "this signaling pathway provides new opportunities for the treatment of type 2 diabetes" (1) may be debatable because the impacts of systemic β_2-adrenoreceptor activation on glucose control and hemodynamic changes are not considered.

Increased sympathetic nervous system activity (exercise and the fight or flight response, as Sato et al. mentioned) is associated not only with increased glucose uptake by skeletal muscle but also with increased hepatic glycogenolysis and/or glucagon release, likely leading to an increase in plasma glucose levels. Plasma glucose and glucagon levels can increase significantly during exercise despite increased glucose uptake in exercising muscle. We recently demonstrated that traumatic injury rapidly increased plasma glucose levels via β_2-adrenoreceptor–dependent glycogenolysis in the liver. Treatment with a selective β_2-adrenoreceptor antagonist blunted the hepatic glycogenolysis and the increase in plasma glucose levels (3). Thus, following systemic β_2-adrenoreceptor activation, the beneficial effect from increased peripheral glucose uptake in skeletal muscle may be overridden by simultaneous increases in hepatic glycogenolysis and/or glucagon release. Notably, due to insulin resistance, obese rats exhibited exacerbated post-trauma hyperglycemia as compared with lean Zucker rats (3). Therefore, the net increase in plasma glucose following β_2-adrenoreceptor activation could be more profound in obesity and type 2 diabetes.

Sato et al. (1) showed that systemic treatment with β_2-adrenoreceptor agonist improved glucose tolerance in diabetic rats and obese mice. However, whether this is due to the same mechanism (mTORC2 pathway) as demonstrated in their in vitro experiments is uncertain. For example, β_2-adrenoreceptor activation also causes arteriolar dilation and capillary recruitment in skeletal muscle and thus increases tissue perfusion and (insulin-mediated) glucose uptake (4). Although the current study eloquently provided evidence for β_2-adrenoreceptor–mediated glucose uptake in skeletal muscle via the cAMP-mTORC2-GLUT4 pathway at the cellular level, future studies are needed to determine the interactions between cellular and systemic glucose responses following β_2-adrenoreceptor activation.

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