

P024 PKC epsilon deletion or inhibition in mice improves lipid-mediated glucose intolerance by restoring glucose-stimulated insulin secretion and by reducing insulin clearance
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Insulin resistance and Type 2 diabetes are strongly associated with lipid oversupply. While the mechanisms involved are unclear, roles for lipid-activated protein kinase C (PKC) isoforms in the generation of skeletal muscle insulin resistance have been suggested by several correlative studies. We have now shown that glucose tolerance is greatly improved in fat-fed PKC ϵ knockout mice compared to wildtype littermates. Surprisingly, this was not associated with improved muscle insulin action, but rather an enhanced availability of insulin, involving two distinct effects. Firstly, although PKC ϵ deletion did not affect insulin secretion in wildtype mice or in isolated islets, it restored glucose-induced secretion in fat-fed animals, and in islets chronically exposed to fatty acids. Secondly, we found that PKC ϵ ablation decreased whole-body insulin clearance, which was supported by diminished insulin uptake by PKC ϵ -deficient hepatocytes. Insulin availability and glucose tolerance were also improved by treatment of obese, diabetic *db/db* mice with a cell-permeant PKC ϵ -inhibitory peptide. Inhibition of PKC ϵ , in liver and pancreatic islets, could therefore represent a novel synergistic therapy for Type 2 diabetes.