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Inducible deletion of protein kinase Map4k4 in obese mice improves insulin sensitivity in liver and adipose tissues.

Danai LV[1], Roth Flach RJ[1], Virbasius JV[1], Garcia Menendez L[1], Jung DY[1], Kim JH[1], Kim JK[2], Czech MP[3].

Author information

Abstract

Studies in vitro suggest that mitogen-activated protein kinase kinase kinase kinase 4 (Map4k4) attenuates insulin signaling, but confirmation in vivo is lacking since Map4k4 knockout is lethal during embryogenesis. We thus generated mice with floxed Map4k4 alleles and a tamoxifen-inducible Cre/ERT^2 recombinase under the control of the Ubiquitin C promoter to induce whole-body Map4k4 deletion after these animals reach maturity. Tamoxifen administration to these mice induced Map4k4 deletion in all tissues examined, causing decreased fasting blood glucose concentrations and enhanced insulin signaling to AKT in adipose tissue and liver, but not skeletal muscle. Surprisingly, however, mice generated with conditional Map4k4 deletion in adiponectin-positive adipocytes or in albumin-positive hepatocytes displayed no detectable metabolic phenotypes. Instead, mice with Map4k4 deleted in Myf5-positive tissues, including all skeletal muscles tested, were protected from obesity-induced glucose intolerance and insulin resistance. Remarkably, these mice also showed increased insulin sensitivity in adipose tissue but not skeletal muscle, similar to the metabolic phenotypes observed in inducible whole-body knockout mice. Taken together, these results indicate that, 1.) Map4k4 controls a pathway in Myf5-positive cells that suppresses whole-body insulin sensitivity and 2.) Map4k4 is a potential therapeutic target for improving glucose tolerance and insulin sensitivity in type-2 diabetes.

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