The significance of GSK-3 in insulin release and glucose metabolism.

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Introduction

Deregulation of the Glycogen Synthase Kinase 3 (GSK-3) protein kinase has been linked to the development of type 2 diabetes. In diabetes, GSK-3 protein expression and kinase activity are increased, and selective GSK-3 inhibitors have showed promise as glucose metabolism and insulin sensitivity modulators. In mammals, there are two GSK-3 isoforms: GSK-3 and GSK-3. Mice lacking GSK-3 perish from liver apoptosis in late embryogenesis, whereas mice lacking GSK-3 are alive and have better insulin sensitivity and hepatic glucose homeostasis [1].

A conditional gene-targeting technique was used to examine the potential role of GSK-3 in insulin action, in which mice with GSK-3 expression specifically ablated within insulin-sensitive tissues were created. GSK-3 deletion mice in the liver are alive, glucose and insulin tolerant, and have normal metabolic and insulin signaling properties. Mice lacking GSK-3 expression in skeletal muscle are also alive, but show superior glucose tolerance as well as insulin-stimulated glycogen synthase regulation and glycogen deposition, in contrast to liver-deleted mice. These findings suggest that GSK-3 and GSK-3 have unique roles in adults, as well as tissue-specific phenotypes associated with each of these isoforms. Glycogen Synthase Kinase 3 (GSK-3) is a highly conserved, widely expressed serine/threonine protein kinase that is divided into two isoforms: GSK-3 and GSK-3, which are encoded by separate genes and produce highly homologous proteins that differ only in their N- and C-terminal regions. GSK-3 is highly active at rest and is rapidly inactivated by insulin through phosphorylation of a serine residue in the N-terminal domain.

The activation of phosphatidylinositol 3-kinase and protein kinase B is required for insulin inhibition of GSK-3, with PKB/Akt phosphorylating both isoforms of GSK-3 on key regulatory serine residues. GSK-3 was first discovered as a Glycogen Synthase (GS) regulator (a rate-limiting enzyme that increases glycogen deposition). Active GSK-3 phosphorylates four serine residues in the C-terminal domain of GS and inhibits its function in the absence of insulin, limiting the capacity of cells to produce and store glycogen. Insulin inhibits GSK-3 (through Ser 9/21 phosphorylation), which causes GS to be dephosphorylated and activated, resulting in higher glycogen production rates [2].

The impairment of both basal and insulin-stimulated glucose metabolism in insulin-responsive, peripheral tissues, such as Skeletal Muscle (SM) and liver is a key characteristic of Type 2 Diabetes Mellitus (T2DM). While there are no known disease-causing mutations in the two GSK-3 genes, there is evidence that GSK-3 expression and activity are increased in the SM of T2DM patients and in the adipose tissues of obese diabetic mice. Furthermore, transgenic overexpression of GSK-3 in the SM of mice causes decreased glucose tolerance and higher blood glucose levels. Reduced glycogen content and increased insulin levels in the blood. GSK-3 inhibitors, on the other hand, can mimic insulin action in cell lines and tissues, and administration of GSK-3 inhibitors to rodent models of obesity and T2DM improves insulin sensitivity and glucose homeostasis by increasing glycogen synthesis while simultaneously inhibiting hepatic gluconeogenesis, improving insulin sensitivity and glucose homeostasis.

While pharmacologic inhibitors of GSK-3 are unable to distinguish between the two isoforms, these medicines cannot be used to assess isoform-specific activities of GSK-3 and GSK-3. Mouse models, on the other hand, have revealed evidence for isoform-specific functions. Mice with GSK-3 deficiency (but still have GSK-3) perish during development. Mice with GSK-3 deficiency (but not GSK-3) are alive and have better whole-body glucose tolerance and hepatic insulin sensitivity. Furthermore, insulin control of GS in the SM of homozygous "knock-in" mice expressing an insulin-insensitive mutant (S9A) of GSK-3 is entirely abolished, whereas GS activity is unaffected in GSK-3 (S21A) knock-in mice. These data show that GSK-3 and GSK-3 isoforms play tissue- and isoform-specific functions in glucose metabolism regulation [3].

We used a conditional gene-targeting method to generate mice that selectively lack GSK-3 expression in two main insulin-sensitive organs, due to the embryonic mortality of global GSK-3 knockout (KO) mice. We show that GSK-3 knockout animals with liver-specific and SM-specific phenotypes have distinct glucose metabolism characteristics. While animals with a Liver-Specific GSK-3 Knockout (LKO) had normal metabolic parameters, mice with an SM-specific GSK-3 Knockout (MKO) had enhanced glucose tolerance and more effective GS activation. The GSK-3 tissue-specific KO mice give novel genetic tools for studying the isoform- and tissue-specific roles of GSK-3 in cellular regulation, as well as a more thorough assessment of the therapeutic potential of GSK-3 inhibitors in the treatment of T2DM [4].

GSK-3-targeting vector generated

A lambda phage clone library containing genomic DNA from the mouse strain 129/Ola was used to identify the genomic

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region flanking exon 2 of the GSK-3 gene. The targeting vector's "arms" of homology were produced using Platinum Pfx PCR amplification of the GSK-3 genomic regions and put into the backbone targeting vector pSPUC. The neomycin resistance cassette was inserted and bordered by FLP recombination target (FRT) sites, whereas LoxP sites were added by PCR into the intrinsic region bordering exon 2 of the GSK-3 gene. The fragments were sequenced to see if there were any PCR-related mistakes [5].

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