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LAY ABSTRACT

Diabetes and mechanism of insulin action: Diabetes mellitus is the most common metabolic disease, affecting over 150 million people worldwide. Diabetes occurs due to a breakdown in the body's ability to regulate glucose levels. A number of tissues are involved in this fine regulation. The pancreas produces a hormone called insulin that acts on several tissues to maintain glucose levels. Resistance to insulin's actions leads to the development of diabetes. Thus maintaining normal glucose levels involves synergistic interactions between various peripheral insulin-responsive tissues. Insulin acts by binding to the insulin receptor at the cell surface, leading to its activation. The activated receptor subsequently acts on several proteins, altering their function through the addition of a phosphate to their tyrosines. This leads to the transmission of insulin's signal inside the cell. Therefore, molecules that affect the phosphate level on tyrosines, either through raising or lowering it, will have profound effects on insulin's signaling.

Protein-tyrosine phosphatases and regulation of insulin signaling: Numerous studies implicated enzymes called protein-tyrosine phosphatases (PTPs) in insulin signaling. PTPs work to remove a phosphate group from tyrosine within another protein hence affecting its function. Recent animal studies identified protein-tyrosine phosphatase 1B (PTP1B) as a physiological regulator of insulin signaling. Extrapolating these findings to humans suggests that PTP1B inhibitors will be useful to improve insulin sensitivity in diabetic humans. These exciting findings suggested that other PTPs are potential targets for the treatment of type 2 diabetes.

Src homology Phosphatase 2 and insulin signaling: A number of studies suggested a role for a PTP, termed Src homology phosphatase 2 (Shp2) in regulating insulin signaling. However, studies in mouse models have provided a mixed picture. Genetically engineered mice that lack Shp2 die before birth. In addition, mice that expressed a mutant Shp2 (that lacks enzyme activity) were insulin resistant. Although this study suggests a role for Shp2 in the regulation of insulin function, the effects of the mutant Shp2 are difficult to interpret since a mutant enzyme could interfere with other molecules. Thus, the precise physiological role of Shp2 in regulating insulin sensitivity and glucose levels is controversial and needs to be resolved. Uncovering the role of Shp2 in this process will potentially provide new targets for the treatment of type 2 diabetes.

Project Goals and Objectives: *The goal is to determine the physiological role of Shp2 in regulating insulin sensitivity and the effects of its deficiency on high fructose feeding*. To study the role of Shp2 in insulin signaling, it will be deleted specifically in individual tissues through genetic engineering approaches. This elegant approach has already been successfully used to dissect the tissue-specific role of insulin receptor in insulin signaling. Thus, mice were generated, where the gene encoding Shp2 protein is flanked by specialized DNA sequences (termed "floxed" mice). These DNA sequences serve as docking sites for an enzyme called Cre-recombinase. When the floxed mice are mated to mice that express Cre-recombinase in specific tissues, the Cre binds to the specific DNA sequences and deletes Shp2 selectively in that tissue. Indeed, we have already generated mice that have specific Shp2 deletion in the liver and the same approach will be used to delete Shp2 in fat. These mice will be valuable tool in dissecting the role of Shp2 in the regulation of insulin signaling and glucose levels. In addition, these mouse models will be utilized to address major nutritional issues. Fructose consumption is a significant proportion in the American diet (largely due to increased consumption of soft drinks and beverages that are rich in fructose). Animal studies show that high fructose consumption leads to increased adiposity and insulin resistance. The molecular basis for these effects is not known but some studies suggest that PTPs (including Shp2) are involved in this signaling process. Therefore, these mice will be used to directly test the effect(s) of Shp2 deletion on high fructose intake. Deleting Shp2 is specific tissues might increase the tyrosine phosphorylation of key components in the pathway and diminish the insulin resistance induced by high fructose feeding. ***Collectively, these studies will advance our molecular understanding of the effects of high fructose intake, insulin signaling and potentially provide new targets for the treatment of obesity and diabetes.***