


Spring 4-2014

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Cotton, JaLise Maree, "Inhibition Mechanisms of Type 2 Diabetes" (2014). *Thinking Matters Symposium Archive*. 8.

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Inhibition Mechanisms of Type 2 Diabetes

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Abstract

Type 2 Diabetes (T2D) is the most common form of diabetes mellitus which affects approximately 8.3% of the population (diabetes.org 2013). T2D is most often brought on by reduced sensitivity to insulin receptors. This is thought to be caused by a mutation in the gene Insulin Receptor Substrate-1 (IRS-1). It is the suppression of IRS-1 that leads to inactivation of signaling molecules insulin signaling pathways causing insulin resistance (Victor D. H. et al). This literature review will focus on the major mechanisms of inhibition of the insulin signaling pathways. Mice that were bred lacking the Akt2 signaling pathway (associated with IRS-1 gene) revealed age-dependent adipose tissue loss and an increase in hyperglycemia. This suggests that the Akt2 pathway is crucial for glucose metabolism (Garofalo 2003; Guo 2013). Future research will focus on activating IRS-1 and Akt2 as a therapeutic modality for the treatment and prevention of type 2 diabetes and other metabolic diseases.

Pathophysiology of Diabetes

- Insulin and glycogen are hormones produced in the pancreas and are the two main hormones involved in regulating the level of glucose in the blood.
- The pancreas contains about 1 million groups of cells called islets. There are two kinds of pancreatic islets: α (alpha) and β (beta) cells. Alpha cells secrete glucagon and β cells secrete insulin.
- On a molecular level glucose homeostasis is triggered by a signaling cascade
- Akt2/IRS-1>FOXO1>PEPCK
- T2D results from a combination of increased insulin resistance due to reduced sensitivity to insulin receptors (i.e. IRS-1) and prolonged deterioration of β cell function.

IRS-1 and Akt2 Signaling Pathways

- Mice were bred lacking Akt2 signaling pathways which are associated with the IRS-1 gene.
- At 22 weeks of age loss of adipose (fat) tissue, increase in hyperglycemia (high blood sugar), and increased insulin resistance were observed.
- This suggests that the degradation of the Akt2 signaling pathways causes the sensitivity of insulin receptors (e.g. IRS-1) to be reduced
- This may be an important step in the development of insulin resistance/diabetes.

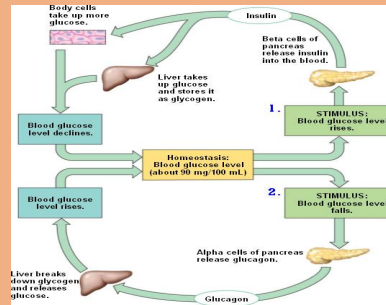


Fig. 1 Glucose Homeostasis nicerweb.com 2014

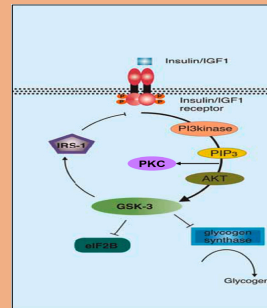


Fig.2 Diagram of normal insulin signaling pathway . Molecular Psychiatry 2008

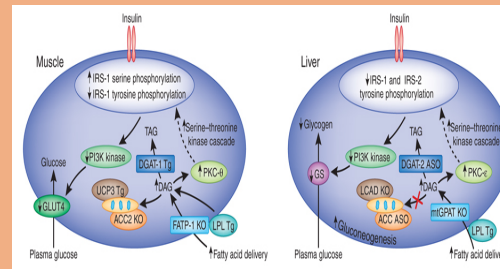


Fig. 3 Comparison of inhibited signaling pathway Naturemedicine.com 2010

Inactivation of the Insulin Growth Factor -1 (IGF-1)

- Insulin receptors and IGF-1 signaling affect pancreatic β cell functions in different ways via their actions on the IRS-1 and IRS-2.
- Mice were bred that lacked both the IGF-1 receptor in pancreatic β cells and either the IRS-1 or IRS-2.
- It was observed that the IGF-1/IRS-2 double mutants that by six weeks of age, the lack of the IGF-1 receptor function aggravated the effects of IRS-2 knockout resulting in diabetes.
- Inactivation of IGF-1/IRS-1 in pancreatic β cells impairs insulin secretion.
- Inactivation of IGF-1/IRS-2 impairs pancreatic β cell replication.

Mutation in FOXO and PEPCK Gene(s)

- PEPCK Gene-(phosphoenolpyruvate carboxykinase) encodes for synthesis of glucose into the bloodstream.
- FOXO1 Gene- the transcription factor that promotes the expression of the PEPCK gene by binding to it.
- β cell –specific deletions on mice using Cre/ loxP-mediated recombination were used to assess FOXO-1 requirement in β cells.
- Deletion of FOXO-1 inhibits the transcription of PEPCK gene suppressing insulin production.

Next Steps/Future Research

- Activating IRS and Akt2 for future treatment and prevention of diabetes (Garofalo 2003; Guo 2013)
- Demonstrate how signaling pathways can be modulated unfolding β cell failure (Shouhong et al 2010).

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Acknowledgements

Remember to thank your classmates, mentors other professors who contributed or supported your work. Mention any grants or fellowship that supported your work. This can also be in a smaller font.

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