Insulin, glucagon and diabetes mellitus

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Lecture Outline

This lecture will cover the roles of insulin and glucagon in normal and pathophyiological states, especially diabetes. It will focus on pharmacological interventions for both of these pathologies. This lecture will cover the following four topics.

- Physiological regulation of blood glucose
- Insulin Signaling
- Glucagon Signaling
- Pathophysiology related to glucose control
  - Type I Diabetes
  - Type II Diabetes
- Common Pharmacological Interventions for Insulin Resistance

Diabetes in the United States.

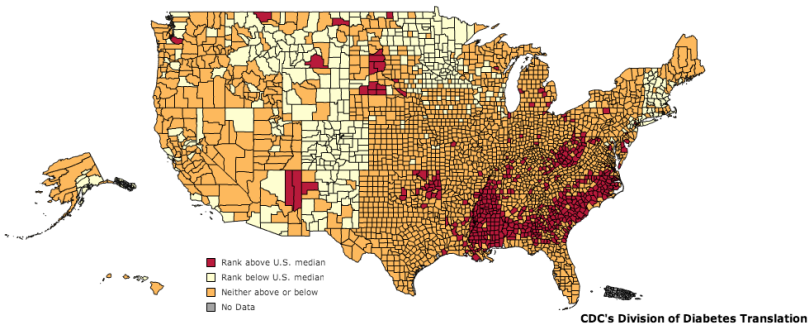

Figure 1: County Level Prevalence in Type II Diabetes

As of 2011, diabetes affects 25.8 million people or 8.3% of the population. This includes approximately 7 million undiagnosed individuals. In addition to this, 79 million Americans over the age of 20 are estimated to be pre-diabetic. As of 2007, diabetes is estimated to cost $116 billion in direct and $58 billion in indirect costs (CDC 2011).

Diabetes is especially prevalent in this region. As shown in the map, there is a higher percentage of diabetics in the mid and deep south regions of the United States.

Acute regulation of circulating glucose

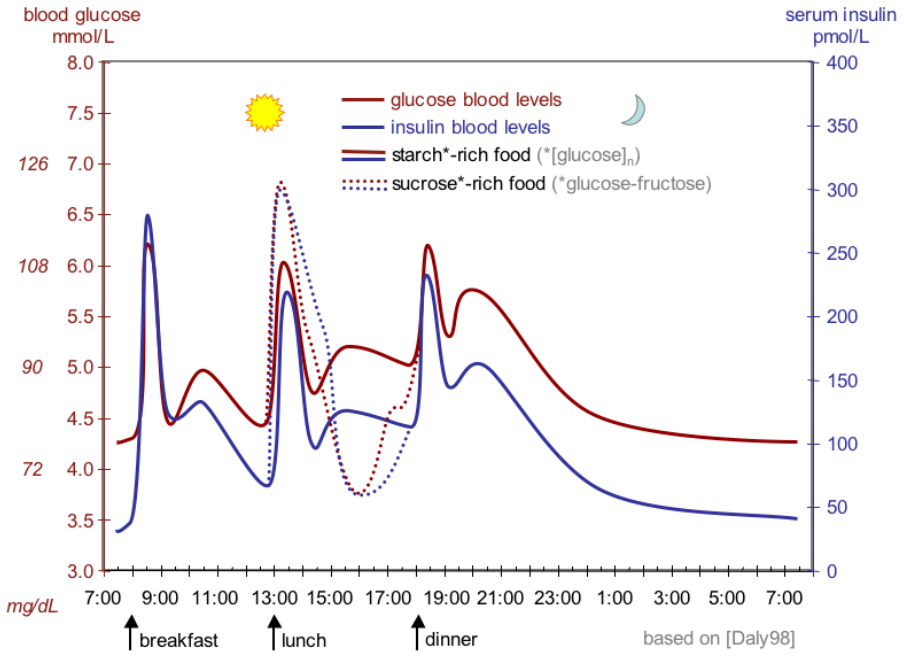

Figure 2: Schematic of glucose and insulin levels throughout the day. (Suckale and Solimena 2008).

Glucose is maintained in a very narrow range, between 4.4 to 6.1 mmol/L. These levels need to be re-established after changes in feeding status, or energy utilization. In general, when glucose levels decrease, glucagon is released from alpha cells of the pancreas to promote glucose production, either from glycogen breakdown or gluconeogenesis. Alternately, after a meal when glucose levels increase, insulin is secreted from beta cells of the pancreas causing glucose levels to decrease.

Mechanisms of glucose control

For the purposes of the acute maintenance of glucose homeostasis, four organs are the most important; the pancreas, liver, muscle and adipose tissue. The pancreas senses changes in glucose levels and responds by releasing either glucagon or insulin.

Insulin Signaling

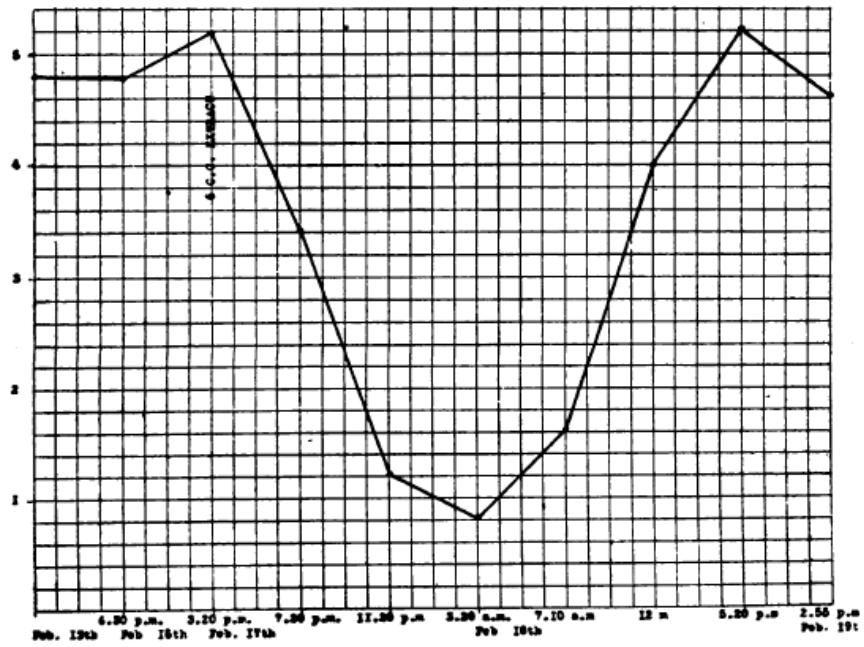

CHART III.—*Effect of one injection of extract on Blood Sugar (mgs. per c.c.e=tenth per cent)*

Figure 3: Effects of a dog pancreas isolate on blood glucose levels in a 14 year old diabetic child (F.G. Banting et al. 1922).

Insulin was discovered by Frederick Banting and his colleagues at the University of Toronto in 1921. They performed experiments in which they injected extracts from pancreas fractions into dogs which had their pancreas' surgically removed. They showed that a secreted substance from the pancreas lowered blood glucose in these dogs (Frederick G. Banting and Best 1922). They were then able to confirm that this treatment was also effective in children with diabetes (F.G.

Banting et al. 1922). This work led to Banting and John Macleod winning the Nobel Prize in Medicine and Physiology in 1923.

Insulin Secretion

Physiological effects of insulin

When glucose levels are raised, such as after a meal, insulin has four main functions:

1. Promotes the uptake of glucose from the blood into muscle and adipose tissue.

2. Enhances the synthesis of glycogen in liver, adipose and muscle.

3. Accelerates the synthesis of triglycerides in fat, and to a lesser extent muscle and liver.

4. Insulin inhibits gluconeogenesis, or the production of glucose from non-glucose precursors such as amino acids and lipids.

Insulin signal transduction

Glucagon Signaling

Physiological effects of glucagaon

When glucose levels are low, glucagon promotes the breakdown of glycogen stores in liver and muscle, and the generation of glucose from gluconeogenic precursors primarily in the liver.

Regulation of glucagon release

Effects of glucagon on the liver

Consequences of dysfunctional glucose homeostasis

Hypoglycemia

- Feinting, dizziness
- Diabetic ketoacidosis

Hyperglycemia

- Chronic hyperglycemia leads to glycation of membrane proteins. This leads to damaged nerves, kidneys, eyes, circulatory system (amputation) and Alzheimer's disease.
- Hyperglycemic hyperosmolar nonketotic syndrome.

Pathophysiology related to glucose control

Type I Diabetes Mellitus

Loss of Insulin Producing Cells

Insulin Administration

The amino acid sequence of insulin was determined by Frederick Sanger, which led to him winning the Nobel Prize in Chemistry in 1958 (Sanger and Tuppy 1951). This eventually allowed for recombinant production and manipulation of insulin, rather than using purified porcine, ovine or bovine insulin.

Short and Long Acting Insulin

Insulin Pumps

Insulin Resistance and Type II Diabetes Mellitus

Mechanisms Underlying Insulin Resistance

- Inflammatory mediators of insulin resistance
- Mediation of insulin resistance by mTORC1

Adaptations to Insulin Resistance

- Hyperinsulinemia
- Pancreatic Failure

Other Control Circuits Related to Glucose Control

- Regulation of food intake
- Hypothalamic regulation of glucose release
- Counterinflammatory responses

Common Pharmacological Interventions for Insulin Resistance

- Primary intervention is diet and exercise alteration

Insulin sensitizers

- Thiazolidinediones
- Mechanism of action

Insulin secretagogues:

- Sulfonylureas

Glucose Utilization

- Metformin
- Mechanism of action

Potential Future Interventions for Insulin Resistance

Generation of Beige Fat

Anti-inflammatory Interventions

Further Reading

Banting, F. G., C. H. Best, J. B. Collip, W. R. Campbell, and a a Fletcher. 1922. "Pancreatic Extracts in the Treatment of Diabetes Mellitus." *Canadian Medical Association Journal* 12 (3) (mar): 141–6. http://www.ncbi.nlm.nih.gov/pubmed/17580419.

Banting, Frederick G., and Charles H. Best. 1922. "The Internal Secretion of the Pancreas." *Journal of Laboratory and Clinical Medicine* 7: 251–266.

CDC. 2011. "National Diabetes Fact Sheet , 2011." http://www.cdc.gov/diabetes/pubs/factsheet11.htm.

Sanger, F., and H. Tuppy. 1951. "The Amino-acid Sequence in the Phenylalanyl Chain of Insulin. I. The Identification of Lower Peptides from Partial Hydrolysates." *The Biochemical Journal* 49 (4) (sep): 463–81. http://www.ncbi.nlm.nih.gov/pubmed/14886310.

Suckale, Jakob, and Michele Solimena. 2008. "Pancreas Islets in Metabolic Signaling–focus on the Beta-cell." *Frontiers in Bioscience : a Journal and Virtual Library* 13 (jan): 7156–71. http://www.ncbi.nlm.nih.gov/pubmed/18508724.