Week 4-Glucose Metabolism and Pharmacology
Liver and Muscles

Glycogen

Glycogenolysis

blood glucose

Glycogenesis

glucose 1-P

Glycolysis

glucose 6-P

Gluconeogenesis

pyruvate

Glycolysis

Link Reaction

Fatty Acid Synthesis

Lipogenesis

Liver and Kidneys

fatty acid

Beta oxidation

Lipolysis

Adipocytes

triglyceride

Signals to Liver and Kidneys

ketogenic aa

Ketone breakdown

Ketogenesis

ketone bodies

Gluconeogenesis

Citric Acid Cycle

αKG

CO₂

http://bvetmed1.blogspot.com/2013/03/energetics-glucose-metabolism-and.html
When the system goes awry...

- **Type-1 diabetes (juvenile onset)**
  - Autoimmune reaction against the insulin-producing beta cells of the pancreas
  - No insulin can be produced

- **Type-2 diabetes (adult onset)**
  - Increased resistance to insulin in the muscles, liver, and adipose tissue in addition to decreased insulin production from pancreatic beta cells
Classes of Anti-Diabetic Drugs

- Insulin
- Sensitizers (decrease insulin resistance)
- Sulfonylureas (directly increase insulin output from the pancreas)
- Alpha-Glucosidase Inhibitors (slows starch digestion in the small intestine)
- Peptide Analogs (indirectly increase insulin output from the pancreas)
Insulins

• Fast-acting (e.g. Humalog, Novalog)

• Intermediate-acting (e.g. Humulin, Novolin)

• Slow-acting (e.g. Lantus, Levemir)
  – This class of insulin analogs is created as insulin microcrystals, which will slowly release insulin and mimic the pancreas’ basal production of insulin
Basal vs. Bolus Insulins

**Basal Insulins** are designed to work slower over a long period of time.

**Bolus Insulins** are designed to work faster over a small period of time (typically post-meal).
Hemoglobin A1C Test

http://guardianlv.com/2013/10/blood-sugar-levels-may-affect-hippocampus-and-memory-says-study/

http://drugline.org/medic/term/a1c/
Sensitizers

• Biguanides (e.g. Metformin)
  – Complete mechanism not understood, but decreases hepatic gluconeogenesis and peripheral insulin resistance by increasing AMPK signaling
  – Typical A1C decrease from 1.5-2%

• Thiazolidinediones (e.g. Pioglitazone)
  – Agonists for PPARs, which are regulatory proteins for genes involved in glucose metabolism, resulting in more efficient glucose usage
  – Typical A1C decrease from 1.5-2%
Sulfonylureas (e.g. Glimepiride, Glyburide)

- Block K-ATP channels on beta cells
- Prevents hyperpolarization and activates Ca+2 channels
- Stimulates insulin vesicle exocytosis
- Typical A1C decrease from 1-2%

http://www.clinicalcorrelations.org/?p=500
Alpha-Glucosidase Inhibitors

• Ex. Acarbose, Miglitol, etc.
• Saccharides that act as competitive inhibitors of the enzyme located on the brush border of the small intestine
• Slows the digestion and metabolism of carbohydrates
• Typical A1C decrease from 0.5-1%
GIP

Incretin, GLP-1

Stimulates insulin release

Inhibits glucagon release

Lowering of blood glucose

DPP-4 enzyme inactivates GLP-1

DPP-4 inhibitors (drugs) block DPP-4 and decrease glucose

Peptide Analogs

• GLP Agonists (e.g. Byetta, Victoza)

• GIP Agonists (in trial phases)

• DPP-4 Inhibitors (e.g. Januvia, Onglyza)

• Typical A1C decrease from 0.5-1%