The Pancreas
Why all the fuss?
The Pancreas and Digestive Functions
Pancreatic Secretions

Pancreatic HCO₃⁻ (bicarbonate) secretion
- Secretin is a hormone
  - Secretin from S-cells in duodenum in response to H⁺
  - To pancreas by blood, stimulates bicarbonate secretion by duct cells
  - Bicarbonate flows to small intestine
    - HCO₃⁻ + H⁺ = H₂O + CO₂
  - Negative feedback onto S-cells to decrease amount of secretin secreted

Pancreatic enzymes basics
- Enzymes:
  - Proteases – trypsin, chymotrypsin, carboxypeptidase
  - Lipases, ribonucleases
- Trypsinogen (in.) converted to trypsin by cell-bound enterokinases.
- Trypsin then converts zymogens to active enzymes.

Development
Pancreatic removal
- Mammal – diabetes results
- Bird – No diabetes! Why
- Pancreas becomes more discrete as we move from lower vertebrates up to primates.
- Diverse in macroscopic structure!
- Controlled by parasympathetic and sympathetic inputs but - not primary controls.

The Endocrine Pancreas
Cell types
Alpha cells (20%)– glucagon
Beta cells (75%)– insulin
Delta (5%) - somatostatin
F cells (?) - pancreatic peptide

Chemistry

- Insulin - 51 AA Protein
- Banting and Best
- Sanger (structure)
- Synthesis

Insulin Structure

- Protein
- Alpha and beta chains
- 2 DS bonds

Synthesis and secretion
11.16 p.256

- Preproinsulin
- Proinsulin
- Short AA acid sequence cleaved out to form active insulin.
- C peptide released

Biochemistry of insulin

Transport and Metabolism

- Not bound to a carrier
• 1/2 life is about 5 minutes (2x glucagon)
• Degraded in liver and kidney
• 50% utilized before reaching liver and kidney.
• Liver is primary target.
• Insulinases! - breakdown insulin and glucagon.

**Glucagon**

• 29 AA polypeptide
• No DS bond or sidechains
• Similar to secretin and gastrin GIP and VIP
• Synthesis is from a preprohormone as well.
• Prohormone is split releasing it to the blood
• Very little in blood - short ½ life ½ removed in first pass through the liver.

**The Endocrine Pancreas**

• Insulin
  - Metabolic Effects
    • Liver Cells
    • Muscle Cells
    • Adipose Cells
  - Mechanism of Action of Insulin--Tyr. Kinase

**Function of pancreatic hormones**

• Growth
• Biochemical metabolism
• Insulin and glucagon have opposite effects
• Insulin - anabolic- lowers blood glucose
• Glucagon- catabolic – raises blood glucose
• Effects on lipid and protein depend on biochemical state I-
  increases fat and protein anabolism G-opposite

Start here
Insulin Function

• Liver Cells
  - Increase Protein Synthesis
    • Glycogen synthesis from glucose
    • Increase glucose transport into cells
    • Increase amino acid transport into cells
    • Positive Nitrogen Balance
  - Store Glucose as Glycogen, reduce blood Glucose concentrations

Insulin Function

• Muscle Cell Actions
  - Increase glucose uptake
  - Increase amino acid uptake
  - Increase protein synthesis (enzymes & structural)
  - Decrease protein degradation
  - Increase fatty acid uptake as needed
  - Increase muscle glycogen synthesis

Insulin Function

• Adipose Cell Actions
  - Increase protein synthesis (for lipogenesis)
  - Increase glucose uptake into cells
  - Increase neutral lipid formation (lipogenesis)
  - Decrease neutral lipid degradation (lipolysis)

Glucose Levels Over Time

The Endocrine Pancreas

• Glucagon
  - Stimuli causing release
    • Elevated Glucose
    • Elevated Amino Acids
  - Mechanisms of Glucagon Effects
    • Liver Effects
    • Muscle Effects
    • Adipose Tissue Effects

• Somatostatin
  - Inhibits Insulin
  - Inhibits Glucagon
Glucagon

• Produced in \(\alpha\) cells of pancreas
• 29 amino acid linear molecule
• Circulation via portal blood to Liver

Glucagon
- Bathes Liver with high levels of glucagon
- Binds to liver cell plasma membranes
  • Increases A.C. activity leading to increased cAMP levels and increased Ca++ levels.

• Glucagon actions in the Liver include:
  - Increases Gluconeogenesis
    • Increases every rate limiting enzyme
  - Increases Glycogenolysis
    • If glycogen is present it is mobilized.

Glucagon
• Increases Amino Acid utilization, decreasing plasma amino acid levels & causing increased \(N_2\) in the plasma.
• Increases Hormone Sensitive Lipase
  - Increased lipolysis, increased FFA in plasma
  - Decreases neutral fat stores
• Primary Fasting hormone of man
• I/G fed ratio = 20/1  I/G fasting ratio = 1/3

Stimuli for Insulin Release

• Phase I
  - Gut glucose  Gut Glucagon
  - Pancreatic Insulin (preformed) + C-peptide
    • short-lived 2 - 6 min.
  - Sulfonylureas, Secretin, CCK-PK

• Phase II
  - Blood Glucose  Cell Gluc.  Insulin
  - Lasts as long as blood glucose is elevated (hr)
  - Insulin synthesis & release (not preformed)

Somatostatin (SRIH) Physiology
• Produced in \(\delta\) (D) cells of pancreas and elsewhere in G.I. Tract
(as you know).

- 14 or 28 Amino Acids
- Release stimulated by High Insulin & Glucagon
- SRIH inhibits release of Insulin and Glucagon
- Decreased glucose transport across gut wall
  - decreased gut blood flow

### Glucagon

- Stimuli
  - 1 stimulus is a fall in plasma glucose
  - 2 stimulus is rise in gut glucose
  - 3 stimulus is rise in plasma amino acids

### Weekly Quiz

- Describe all the secretions of the pancreas and give a brief function for each.