Chapter 11 Insulin  
Lecture 16

Pancreas
most of organ: exocrine secretion digestive enzymes & HCO$_3^-$
endocrine cells only 2% of total organ
surrounded by capillaries & parasympathetic/sympathetic

A. Islets of Langerhans
1869 Paul Langerhans German anatomist

B. four cell types
1. β type: 75% cells
   insulin & amylin
2. α type: 20% cells
   glucagon
3. D type: ~5% cells
   somatostatin
4. F (PP) type: ~<1% cells
   pancreatic polypeptide
Chemical Structure of Insulin

Insulin secretion stimulated by:
1) ↑ glucose concentrations
2) ↑ amino acids concentrations
3) feed forward effects of GI hormones
4) parasympathetic activity
5) sympathetic activity

Insulin & Glucagon antagonistic ratio titers determines dominance of hormonal action
a) fed state? insulin

(b) Fasted state: glucagon dominates

Glucagon Stimulates

↑Glucose oxidation
↑Glycogen synthesis
↑Fat synthesis
↑Protein synthesis

Glucagon Stimulates

↑Glycogenolysis
↑Gluconeogenesis
↑Ketogenesis

Chemical Structure of Insulin
Fed State

- ↑ Plasma glucose
- β cells of pancreas
- α cells of pancreas
- ↑ Insulin
- Liver
  - ↑ Glycolysis
  - ↑ Glycogenesis
  - ↑ Lipogenesis
- Muscle, adipose, and other cells
  - ↑ Glucose transport
- ↓ Plasma glucose
  - Negative feedback

Starved State: hypoglycemia

- ↓ Plasma glucose
- β cells of pancreas
- ↓ Insulin
- α cells of pancreas
- ↑ Glucagon
  - Liver, pyruvate, amino acids
  - Fatty acids
  - Prolonged hypoglycemia
- Glycogenolysis
- Gluconeogenesis
- Ketones
  - For use by brain and peripheral tissues
  - Negative feedback
Glucagon-glucose-insulin titers over 24 hr period

Normal & Abnormal Results of Glucose Tolerance Test
Insulin: Cellular Mechanism of Action

1. Insulin binds to tyrosine kinase receptor.

2. Receptor phosphorylates insulin-receptor substrates (IRS).

Nucleus

Extracellular fluid

Insulin
Insulin: Cellular Mechanism of Action

1. Insulin binds to tyrosine kinase receptor.
2. Receptor phosphorylates insulin-receptor substrates (IRS).
4. Membrane transport is modified.

Insulin binds to tyrosine kinase receptor.
Receptor phosphorylates insulin-receptor substrates (IRS).
Second messenger pathways alter protein synthesis and existing proteins.
Membrane transport is modified.
**Insulin: Cellular Mechanism of Action**

1. Insulin binds to tyrosine kinase receptor.
2. Receptor phosphorylates insulin-receptor substrates (IRS).
4. Membrane transport is modified.
5. Cell metabolism is changed.

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**Insulin: promotes anabolism**

1. ↑ glucose transport into most, but not all, insulin-sensitive cells
2. enhances cellular utilization & storage of glucose
3. enhances utilization of amino acids
4. promotes fat synthesis
Insulin promotes cellular glucose uptake

**without insulin**

**with insulin**

(a) Hepatocyte in fed state: liver cell takes up glucose.

(b) Hepatocyte in fasted state: liver cell makes glucose and transports it out into the blood.

Insulin acts **indirectly** to alter glucose uptake in hepatocytes
Summary of Insulin

<table>
<thead>
<tr>
<th>Cell of origin</th>
<th>Beta cells of pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical nature</td>
<td>51-amino acid peptide</td>
</tr>
<tr>
<td>Biosynthesis</td>
<td>Typical peptide</td>
</tr>
<tr>
<td>Transport in the circulation</td>
<td>Dissolved in plasma</td>
</tr>
<tr>
<td>Half-life</td>
<td>5 minutes</td>
</tr>
<tr>
<td>Factors affecting release</td>
<td></td>
</tr>
<tr>
<td>Plasma [glucose] &gt; 100 mg/dL;</td>
<td></td>
</tr>
<tr>
<td>↑ blood amino acids; GLP-1</td>
<td></td>
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<tr>
<td>(feedforward reflex); and</td>
<td></td>
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<tr>
<td>parasympathetic activity amplifies.</td>
<td></td>
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<tr>
<td>Sympathetic activity inhibits.</td>
<td></td>
</tr>
<tr>
<td>Target cells or tissues</td>
<td>Liver, muscle, and adipose tissue</td>
</tr>
<tr>
<td>Target receptor</td>
<td>Membrane receptor with tyrosine kinase activity; pathway with insulin-receptor substrates</td>
</tr>
<tr>
<td>Whole body or tissue action</td>
<td></td>
</tr>
<tr>
<td>Plasma [glucose] by ↑ transport into cells or ↑ metabolic use of glucose</td>
<td></td>
</tr>
<tr>
<td>Action at cellular level</td>
<td></td>
</tr>
<tr>
<td>↑ Glycogen synthesis; ↑ aerobic metabolism of glucose; ↑ protein and triglyceride synthesis</td>
<td></td>
</tr>
<tr>
<td>Action at molecular level</td>
<td></td>
</tr>
<tr>
<td>Inserts GLUT transporters in muscle and adipose cells; alters enzyme activity. Complex signal transduction pathway involved.</td>
<td></td>
</tr>
<tr>
<td>Feedback regulation</td>
<td></td>
</tr>
<tr>
<td>↓ Plasma [glucose] shuts off insulin release.</td>
<td></td>
</tr>
<tr>
<td>Other information</td>
<td>Growth hormone and cortisol are antagonistic.</td>
</tr>
</tbody>
</table>
## Summary of Glucagon

<table>
<thead>
<tr>
<th>Cell of origin</th>
<th>Alpha cells of pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical nature</td>
<td>29-amino acid peptide</td>
</tr>
<tr>
<td>Biosynthesis</td>
<td>Typical peptide</td>
</tr>
<tr>
<td>Transport in the circulation</td>
<td>Dissolved in plasma</td>
</tr>
<tr>
<td>Half-life</td>
<td>4–6 minutes</td>
</tr>
<tr>
<td>Factors affecting release</td>
<td>Stimulated by plasma [glucose] &lt; 200 mg/dL, with maximum secretion below 50 mg/dL; ↑ blood amino acids</td>
</tr>
<tr>
<td>Target cells or tissues</td>
<td>Liver primarily</td>
</tr>
<tr>
<td>Target receptor/second messenger</td>
<td>G protein-coupled receptor linked to cAMP</td>
</tr>
<tr>
<td>Whole body or tissue action</td>
<td>↑ Plasma [glucose] by glycolysis and gluconeogenesis; ↑ lipolysis leads to ketogenesis in liver</td>
</tr>
<tr>
<td>Action at molecular level</td>
<td>Alters existing enzymes and stimulates synthesis of new enzymes</td>
</tr>
<tr>
<td>Feedback regulation</td>
<td>↑ Plasma [glucose] shuts off glucagon secretion</td>
</tr>
<tr>
<td>Other information</td>
<td>Member of secretin family (along with VIP, GIP, and GLP-1)</td>
</tr>
</tbody>
</table>
