The endocrine pancreas
The integrated endocrine control of metabolism.

Gabriella Kékesi

- **62. The endocrine pancreas.**
  - Identify the major hormones secreted from the endocrine pancreas (insulin, glucagon, somatostatin, pancreatic polypeptide, amylin), their cells of origin, and their chemical nature (Langerhans islet). List the major target organs or cell types for insulin, the major effects of insulin on each, and the consequent changes in concentration of blood transport nutrients.
  - Understand the relationship between blood glucose concentrations and insulin secretion. Define the term “incretin” and give examples (GLP-1, GIP). Describe the roles of neural input and gastrointestinal hormones on insulin secretion. Describe the control of glucagon secretion.
  - List the target organs or cell types for glucagon and describe its principal actions on each.
  - Describe the consequences of over-secretion or under-secretion of insulin. Diabetes mellitus: types, symptoms, complications.

- **63. The integrated endocrine control of metabolism.**
  - Identify the normal range of plasma glucose concentrations, and list the chemical forms and anatomical sites of storage pools for glucose and other metabolic substrates.
  - Identify the hormones that promote the influx and efflux of glucose, fat, and protein into and out of energy storage pools and their impact on the uptake of glucose by tissues. Establish specific roles for insulin, glucagon, growth hormone and catecholamines.
Definitions

- **Ketogenesis**: the process by which ketone bodies (acetoacetate, acetone …) are produced as a result of fatty acid breakdown.
- **Gluconeogenesis**: refers to formation of new glucose from glycogenic amino acids, lactate, glycerol and pyruvate.
- **Glycogenolysis**: refers to glycogen breakdown to glucose.
- **Glycolysis**: refers to anaerobic or aerobic breakdown of glucose.
- **Hyperglycaemia**: blood glucose is above 6.7 mM
- **Hypoglycaemia**: blood glucose is below 2 mM

- Transport nutrients are: glucose, FFA, ketonbodies.

Control of energy metabolism

**Challenges**

- Phasic food intake ↔ continuous energy expenditure
- Mismatch between energy uptake and energy consumption
- Cell-specific uptake, storage and mobilization of energy substrates

**Strategies**

- Transport nutrients as energy substrates
- Energy deposits / mobilization
  - Glycogen – liver, muscle
  - fat – adipose tissue
  - Structure proteins
- De novo synthesis of energy substrates
  - Gluconeogenesis, FFA – ketone bodies, glucose – lactic acid)
- Regulatory mechanism
  - endocrine – insulin, glucagon, epinephrine, GH, cortisol, T3/T4
  - neural
    - autonomic (SY, PSY)
    - Hypothalamus (hunger/satiety)
**Muscle cells**

- **Glycogenesis**
- **Glycogenolysis**: glycogen – glucose-6-phosphate – lactate – blood – a) oxidation – heart muscle and b) liver: gluconeogenesis - Cori-cycle
- fasting – poteolysis – aminoacids – **gluconeogenesis** (liver) – blood glucose level stabilization
**Adipose tissue**

- Adipocytes: subcutaneous, visceral, pericardial, perirenal
- Brown vs white
- Triglycerides – energy source
- Hormon transformation, hormon production
  - Leptin – fatty acid oxidation
- Triglycerid synthesis vs lipolysis (hormon-sensitive lipase)

**Liver**

- Vena portae and v. hepaticae
- Glycogenesis vs glycogenolysis
- Gluconeogenesis
- Fatty acid – triglycerid – lipoprotein transformation
- No lipid store (vs adipocytes)
- Lipogenesis (ketogenesis)
**Glucose - Normoglycaemia 4.5-6.2 mmol/L**

- Cells use it primary source of energy and intermediary metabolite
- D-glucose is often referred to as dextrose

**Glucose transport**

**A/ Na⁺-glucose cotransport** (luminal membrane)
- GI-tract
- Kidney

**B/ facilitated diffusion** (basal membrane)
- GLUT 1-6
  - GLUT-1: endothelial cells of BBB, RBC, adipose tissue
  - GLUT-2: renal tubules, brain capillaries, B-cells, intestinal epithelial cells, liver cells
  - GLUT-3: neurons, placenta
  - GLUT-4: adipose tissue cells, striated muscle
    - Insulin dependent, but in case of muscle activity it also translocated
In the epigastrium

- α cell: Glucagon (15-20%)  
- β cell: Insulin (vital); amylin (60-80%)  
- δ cell: Somatostatin - inhibits endocrine function of pancreas (3-10%)  
- PP cell: Pancreatic polypeptide (PP) – inhibits exocrine pancreas (1%)  

Islets of Langerhans
**Discovery of insulin**

1889: Mering and Minkowski
- Remove dog pancreas - diabetes

1921: McLeod laboratory
- Repeat Mering experiment
- Isolated pancreas extract and injection
- Bovine insulin isolation

1922:
- First insulin injection to human

*Frederick Banting & Charles Best
1923 – Nobel prize*

Pre-pro-insulin

<table>
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<th>Signal sequence</th>
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<td>NH₂⁺</td>
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Pro-insulin

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<th>C-peptide</th>
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<td>NH₂⁺</td>
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Insulin

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<th>A chain 21 amino acid</th>
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<tr>
<td>NH₂⁺</td>
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<table>
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<th>B chain 30 amino acid</th>
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<tr>
<td>NH₂⁺</td>
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Zn-complex

© jp herve g y m barcia-macay
1. Cellular rearrangement (s)
Translocation of GLUT transporters into the cell membrane (GLUT4)

2. Change enzyme activity (min)
Phospho-/dephosphorilation (PDE)

3. Gene expression modulation (h)
Decrease the transcription of proglucagon gene
Target cells of insulin

1. Muscle cells
2. Adipose tissue
3. Liver

Muscle

- glucose uptake ↑
  - Physical activity alone (without insulin) also increases glucose uptake!
- glycogenesis ↑
- glycogenolysis ↓
- amino acid uptake ↑
- muscle protein synthesis ↑
- muscle protein conservation
Adipose tissue

- triglycerid level ↑, lypolysis ↓: lipid reservoirs
- endothelial lipoprotein-lipase activity ↑
- hormonsensitive lipase ↓
- glucose uptake ↑, ketone body formation ↓
- Insulin - 25x glucose transport

Liver

- enzyme activity change
- glycogenesis ↑
- fatty acid from glucose↑
- glycogenolysis, gluconeogenesis ↓
- glucose ↓
- ketone body forming enzymes activity↓
Insulin production / regulation

Blood glucose level↑

Amino acids
GI hormones (incretins: GLP, GIP)

PSY (M3)
SY (α2 receptor)

+ + +

A cell
B cell
D cell

Glucagon
Insulin
Somatostatin

Protein synthesis

Blood glucose level↓

Lipid synthesis

„Incretins”

• Metabolic hormones
  • stimulate a decrease in blood glucose levels by
    – causing an increase in the amount of insulin after eating, before blood glucose levels become elevated
    – slow the rate of absorption of nutrients into the blood stream by reducing gastric emptying and may directly reduce food intake.
    – inhibit glucagon release
  • Candidates are:
    • glucagon-like peptide-1 (GLP-1)
    • gastric inhibitory peptide (also known as: glucose-dependent insulino tropic polypeptide or GIP).
Diabetes

I. IDDM = insulin-dependent diabetes mellitus (young)
II. NIDDM = non-insulin-dependent diabetes mellitus (90%)

Diabetes during pregnancy
### 1. IDDM
- **Reason**: Insulin deficiency
- **Age**: Young
- **Body weight**: Normal
- **Occurrence**: Fast
- **B-cell number**: Less than 10%
- **Blood insulin**: Low or absent
- **Autoantibodies**: Yes
- **Ketoacidosis**: Yes
- **Therapy**: Insulin

### 2. NIDDM
- **Reason**: Resistant to insulin
- **Age**: Adult
- **Body weight**: Normal or obese
- **Occurrence**: Slow
- **B-cell number**: Normal then decrease
- **Blood insulin**: High at the beginning
- **Autoantibodies**: No
- **Ketoacidosis**: No
- **Therapy**: Oral antidiabetic (sometimes insulin)

### Procedure and evaluation
- Empty stomach – blood sample
- Glucose solution (75g) within 5 min
- Blood is drawn 3-5 times for glucose and insulin measurements
- It should be maximal within the first hour
- The maximal glucose level can not exceed 10 mM/L
Diagnostics

• HbA1c – glycosylated hemoglobin
• identify the average plasma glucose concentration over prolonged periods of time
• A1c ≥ 48 mmol/mol (≥6.5%) as another criterion for the diagnosis of diabetes (American Diabetes Association)

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Estimated average glucose (mmol/L)</th>
<th>Estimated average glucose (mg/dL)</th>
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<tbody>
<tr>
<td>5.4 (4.2–6.7)</td>
<td>97 (76–120)</td>
<td></td>
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<tr>
<td>7.0 (5.5–8.5)</td>
<td>126 (109–152)</td>
<td></td>
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<tr>
<td>8.6 (6.8–10.3)</td>
<td>154 (123–185)</td>
<td></td>
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<tr>
<td>10.2 (8.1–12.1)</td>
<td>183 (147–217)</td>
<td></td>
</tr>
<tr>
<td>11.8 (9.4–13.9)</td>
<td>212 (170–249)</td>
<td></td>
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<tr>
<td>13.4 (10.7–15.7)</td>
<td>241 (193–282)</td>
<td></td>
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<tr>
<td>14.9 (12.0–17.5)</td>
<td>269 (217–314)</td>
<td></td>
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<tr>
<td>16.5 (13.3–19.3)</td>
<td>298 (240–347)</td>
<td></td>
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</table>

Insulin over production

• Hypoglycaemia (<2 mM)
  • CNS becomes excitable and facilitates neuronal activity: hallucinations, nervousness, trembles
  • Sympathetic activation: sweating, tachycardia, palor, weakness
  • Loss of consciousness, clonic convulsions, hypoglycaemic coma (below 2.8 mmol/L)
Glucagon

- pancreas A cells; GI tract L cells

**Glucagon production / regulation**

- Blood glucose level ↓
  - Amino acids
  - GI hormones
  - SY (β2 receptor)
  - ACh

- Blood glucose level ↑
  - Lipid mobilisation
  - Somatostatin

- Glucagon

- Insulin

- B cell

- A cell

- D cell
Glucagon effects

- glycogenolysis ↑
- gluconeogenesis ↑
- lipid mobilisation (ketogenesis)

Blood glucose level increases

Physiological antagonism: insulin vs glucagon
**Somatostatin**

- Synthesis: pancreas D cells, stomach, intestine, brain
- effects (paracrin)
  - glucagon secretion ↓
  - insulin secretion ↓
- Production / regulation:
  - hyperglycaemia, amino acids, nervous system, CCK

**PP – pancreas polipeptid**

- Synthesis: PP cells
- 1%
- Effect:
  - Exocrin pancreas ↓ (CCK antagonist)
  - Gastric juice production
- Increases PP production: proteins, fasting, exercise, acute hypoglycaemia, vagus activation, gastrin, secretin, CCK
- Decreases PP production: somatostatin
**Amylin**

- Peptide– B-cells
- slowing gastric emptying
- promoting satiety
- preventing post-prandial spikes in blood glucose levels
- inhibition of digestive secretion
- inhibiting secretion of the gluconeogenic hormone glucagon

- reduce the total insulin demand

- apoptotic cell-death in insulin-producing beta cells, an effect that may be relevant to the development of type II diabetes

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Tissue of Origin</th>
<th>Metabolic Effect</th>
<th>Effect on Blood Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Pancreatic β Cells</td>
<td>1) Enhances entry of glucose into cells; 2) Enhances storage of glucose as glycogen, or conversion to fatty acids; 3) Enhances synthesis of fatty acids and proteins; 4) Suppresses breakdown of proteins into amino acids, of adipose tissue into free fatty acids.</td>
<td>Lowers</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Pancreatic δ Cells</td>
<td>1) Suppresses glucagon release from α cells (acts locally); 2) Suppresses release of Insulin, Pituitary tropic hormones, gastrin and secretin.</td>
<td>Lowers</td>
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<tr>
<td>Glucagon</td>
<td>Pancreatic α Cells</td>
<td>1) Enhances release of glucose from glycogen; 2) Enhances synthesis of glucose from amino acids or fatty acids.</td>
<td>Raises</td>
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<td>Epinephrine</td>
<td>Adrenal medulla</td>
<td>1) Enhances release of glucose from glycogen; 2) Enhances release of fatty acids from adipose tissue.</td>
<td>Raises</td>
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<tr>
<td>Cortisol</td>
<td>Adrenal cortex</td>
<td>1) Enhances gluconeogenesis; 2) Antagonizes Insulin.</td>
<td>Raises</td>
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<td>ACTH</td>
<td>Anterior pituitary</td>
<td>1) Enhances release of cortisol; 2) Enhances release of fatty acids from adipose tissue.</td>
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<td>Growth Hormone</td>
<td>Anterior pituitary</td>
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<td>Thyroxine</td>
<td>Thyroid</td>
<td>1) Enhances release of glucose from glycogen; 2) Enhances absorption of sugars from intestine</td>
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Metabolic effect of INSULIN

- **Blood glucose level ↓**
  - Peripheral glucose uptake ↑ (adipose, muscle)
  - glycogenesis ↑ (muscle, liver)
  - glycogenolysis ↓ (muscle, liver)

- **Anabolic properties on protein metabolism**
  - Amino acid uptake in muscles ↑
  - Protein synthesis (muscle)

- **Lipid metabolism**
  - Lipid deposition (adipose tissue)
  - Lipogenesis ↑ (liver)

Metabolic effects of GLUCAGON

- **Blood glucose level ↑** - protects against hypoglycemia
  - Glycogenolysis and gluconeogenesis ↑ (liver)

- **Lipid mobilization**
  - ketogenesis
Metabolic effects of CORTISOL

- **Blood glucose level ↑**
  - Glycogenolysis ↑
  - Gluconeogenesis ↑
- **Catabolic effects on muscles and adipose tissues**
  - Lipolysis, proteolysis, insulin sensitivity ↓
- **Permissive role**
  - Glucagon secretion ↑
  - Potentiates adrenergic effects – receptor density and sensitivity ↑

Metabolic effects of GROWTH HORMONE

adaptation to stress and starvation

- **Blood glucose level ↑**
  - Glucagon secretion ↑
  - Insulin sensitivity of peripheral tissues ↓
- **Anabolic properties**
  - Protein synthesis ↑
- **Permissive role**
  - Potentiates the effects of lipolytic hormones – FFA↑
Metabolic effects of THYROID HORMONES (T3/T4)

- **Calorigenic effect** – BMR
  - Enhanced ionic transports – NA/K pump → increased oxidative processes,
    Number and activity of mitochondria ↑
- **Blood glucose level** ↑
  - Glucose absorption from the GI tract ↑
  - Gluconeogenesis ↑
  - Insulin sensitivity ↓
- **Lipid metabolism** – plasma triglyceride and cholesterol ↓
  - Cholesterol synthesis and metabolism ↑, LDL receptor density ↑
  - Lipolysis in adipose tissue ↑
  - Triglyceride synthesis in liver ↑
- **Permissive role**
  - GH and somatomedine secretion ↑
  - Potentiates adrenergic effects

Metabolic effects of ADRENALIN

- **Blood glucose level** ↑
  - Glycogenolysis in liver and muscle
  - Cori-cycle: muscle – glycogenolysis – lactic acid – liver
    – glucose – blood
- **Lipolysis** ↑
  - Hormone-sensitive lipase ↑
The integrated endocrine control of metabolism

- Mobilization and storage
- Absorptive and postabsorptive phases

- Carbohydrate intake: insulin↑↑ + glucagon↓
- Protein intake: insulin↑ + glucagon↑↑
- Carbohydrate+protein: insulin ↑, glucagon does not change since hyperglykaemia inhibits amino acids induced glucagon secretion

- Postalimentary hypoglykaemia

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Starvation

- Glucose-dependent cells: neurons, RBCs
- Storages (adipocytes, liver, muscle)
- The maximal duration of starvation depends on:
  - gluconeogenesis
  - Triglyceride storages

- Endocrine control:
  - Insulin/glucagon ratio decreases
  - GH secretion increases
  - Glucocorticoids (permissive role – lipolysis, gluconeogenesis, glucagon secretion)
1. **Postabsorptive phase**
   - NORMOGLYKAEMIA
   - **Low** Insulin; glucagon slightly ↑
   - Liver: gluconeogenesis (lactate, glycerine), glicogenolysis
   - Adipocytes: lipolysis↑ - FFA (for skeletal muscle and heart muscle)

2. **24-72 hs short-lasting starvation**
   - HYPOGLYKAEMIA
   - insulin ↓; glucagon & GH ↑↑
   - Gluconeogenesis (lactate, amino acids from muscle proteolysis, glycerin) – urea in urine↑
   - Lipolysis – FFA as energy source!!! Except in the brain and RBCs
   - Ketogenesis (for skeletal muscle and heart muscle)

3. **After 72 hs (depending on the fat storages) Long-lasting starvation**
   - Energy expenditure ↓↓ (20%); reasons:
     - Inactivity, **Thyroid gland ↓, leptin ↓**
     - Insulin ↓ ↓ ↓; GH↑↑ ↑
     - Lipolysis, ketogenesis ↑↑ (neurons also, thus – glucose requirement ↓ - gluconeogenesis ↓)
     - proteolysis ↑↑↑ - destruction (respiratory muscles…)

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