The endocrine pancreas (LO 62)

The integrated endocrine control of metabolism (LO 63)

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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)
**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.**
**Muscle cells**

- **Glycogenesis**
- **Glycogenolysis**: glycogen – glucose-6-phosphate – lactate – blood – a) oxidation – heart muscle and b) liver: gluconeogenesis - Cori-cycle
- fasting – proteolysis – 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, a. hepatica 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
Islets of Langerhans

- 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 polipeptide (PP) – inhibits exocrine pancreas (1%)

**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

Pro-insulin

C-peptide

Zn-complex

Signal sequence

Insulin

A chain
21 amino acid

B chain
30 amino acid

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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

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**Target cells of insulin**

1. Muscle cells
2. Adipose tissue
3. Liver
**Insulin effects on muscle**

- glucose uptake ↑
  - Physical activity alone (without insulin) also increases glucose uptake!
- glycogenesis ↑
- glycogenolysis ↓

- amino acid uptake ↑
- muscle protein synthesis ↑
- muscle protein conservation

**Insulin effects on adipose tissue**

- triglycerid level ↑, lypolysis ↓: lipid reservoires
- endothelial lipoprotein-lipase activity ↑
- hormonsensitive lipase ↓

- glucose uptake ↑, ketone body formation ↓

- Insulin - 25x glucose transport
**Insulin effects on liver**

- enzyme activity change
- glycogenesis $\uparrow$
- fatty acid from glucose $\uparrow$
- glycogenolysis, gluconeogenesis $\downarrow$
- glucose $\downarrow$

- ketone body forming enzymes activity $\downarrow$

**Insulin production / regulation**

![Diagram showing insulin production and regulation](image)

- Blood glucose level $\uparrow$
  - Amino acids
  - GI hormones (incretins: GLP, GIP)
  - PSY (M3)
- Blood glucose level $\downarrow$
  - Insulin
  - Somatostatin
  - Protein synthesis
  - Lipid synthesis

- GLP, GIP, Insulin, Somatostatin, Glycogen, Glucose, Fatty acid, Glucagon, A cell, B cell, D cell, Glucose level, Lipid synthesis, Protein synthesis, GI hormones, PSY (M3), SY ($\alpha_2$ receptor), GI hormones (incretins: GLP, GIP), A cell, B cell, D cell, Insulin, Somatostatin, Blood glucose level, Protein synthesis, 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 bloodstream 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 insulinotropic polypeptide or GIP).

Diabetes

A. I. IDDM = insulin-dependent diabetes mellitus (young)
B. II. NIDDM = non-insulin-dependent diabetes mellitus (90%)
C. Diabetes during pregnancy (3-10%)
  - human placental lactogen ~ GH – maternal insulin-sensitivity ↓;
  - facilitate the energy supply of the fetus; lipolysis; promotes growth
insulin deficiency

lipid mobilisation

glucose uptake ↓ by tissues

glycogenolysis ↑
gluconeogenesis ↑
glycogenesis ↓

IC glucose deficiency  EC glucose excess

keton body formation

hyperventilation „Kussmaul breathing”

metabolic acidosis Nausea, vomiting

glucosuria ↓

glucose uptake ↓ by tissues

polyuria

glycogenesis ↓

gluconeogenesis ↑

glycogenolysis ↑

glucose uptake ↓ by tissues

dehydration ↓

polydipsia

blood volume ↓

Circulation failure

1. IDDM

Reason  Insulin deficiency  Resistant to insulin

Age  young  adult

Body weight  normal  Normal or obese

Occurance  fast  slow

B-cell number  Less than 10%  Normal then decrease

Blood insulin  Low or absent  High at the beginning

Autoantibodies  yes  no

Ketoacidosis  yes  no

Therapy  Insulin  Oral antidiabetic (sometimes insulin)

2. NIDDM
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 (mmol/mol)</th>
<th>estimated average glucose (mmol/L)</th>
<th>(mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5.4 (4.2–6.7)</td>
<td>97 (76–120)</td>
</tr>
<tr>
<td>6</td>
<td>7.0 (5.5–8.5)</td>
<td>126 (100–152)</td>
</tr>
<tr>
<td>7</td>
<td>8.6 (6.8–10.3)</td>
<td>154 (123–185)</td>
</tr>
<tr>
<td>8</td>
<td>10.2 (8.1–12.1)</td>
<td>183 (147–217)</td>
</tr>
<tr>
<td>9</td>
<td>11.8 (9.4–13.9)</td>
<td>212 (170–249)</td>
</tr>
<tr>
<td>10</td>
<td>13.4 (10.7–15.7)</td>
<td>240 (193–282)</td>
</tr>
<tr>
<td>11</td>
<td>14.9 (12.0–17.5)</td>
<td>269 (217–314)</td>
</tr>
<tr>
<td>12</td>
<td>16.5 (13.3–19.3)</td>
<td>298 (240–347)</td>
</tr>
</tbody>
</table>
**Insulin over production**

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

**Glucagon**

- pancreas A cells; GI tract L cells

![Diagram of Glucagon pathway](image)
Glucagon production / regulation

Blood glucose level ↓

Amino acids
GI hormones
ACh
SY (β2 receptor)

B cell → A cell → Glucagon → D cell

Insulin
Glucagon
Somatostatin

Blood glucose level ↑
Lipid mobilisation

Glucagon effects

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

Blood glucose level increases
Physiological antagonism: insulin vs glucagon

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

Somatostatin
**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

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**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
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 hyperglycaemia inhibits amino acids induced glucagon secretion

- Postalimentary hypoglycaemia

<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>
</tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Cortisol</td>
<td>Adrenal cortex</td>
<td>1) Enhances gluconeogenesis; 2) Antagonizes Insulin.</td>
<td>Raises</td>
</tr>
<tr>
<td>ACTH</td>
<td>Anterior pituitary</td>
<td>1) Enhances release of cortisol; 2) Enhances release of fatty acids from adipose tissue.</td>
<td>Raises</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>Anterior pituitary</td>
<td>Antagonizes Insulin</td>
<td>Raises</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>Thyroid</td>
<td>1) Enhances release of glucose from glycogen; 2) Enhances absorption of sugars from intestine.</td>
<td>Raises</td>
</tr>
</tbody>
</table>
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 ↑

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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 ADRENALINE

- **Blood glucose level** ↑
  - Glycogenolysis in liver and muscle
  - Cori-cycle: muscle – glycogenolysis – lactic acid – liver
    – glucose – blood
- **Lipolysis** ↑
  - Hormone-sensitive lipase ↑
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 – no stimulus for insulin secretion
   - 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…)

**Phases of starvation**