Metabolic effects of insulin and glucagon

• structure, biosynthesis, secretion

• insulin dependent/independent tissues, glucose entry into cells

• receptors, signal pathways – biological response

• enzymes regulated by insulin and glucagon

• metabolism at well-fed state and starvation

• Diabetes mellitus
Insulin, glucagon - peptide hormones

**Insulin:**

*structure:* 51 amino acids, 2 polypeptide chains A, B, linked by 2 disulfide bridges

*synthesis:*

β-cells of the islets of Langerhans - exocrine pancreatic cells (1-2%)

inactive precursor

(preproinsulin, linear chain – RER)

↓

cleavage

(proinsulin – removal of signal sequence, formation of –S-S-bonds – ER, release of the C-peptide – Golgi complex)

↓

active hormone - insulin

↓

storage in cytosolic granules

↓

secretion: exocytosis (after stimulation)
**Insulin degradation:**
circulating insulin - biological half-time ~ 6 min
degradation in **liver, kidney** - **insulinase**

bound to receptors in tissues – half-time ~ 7-12 hrs
degradation in **lysosomes** - after internalization of the hormone-receptor complex

**Glucagon:**
**structure:** 29 amino acids – single linear chain

**synthesis:** α-cells of the islets of Langerhans
inactive precursor

(proglucagon – large polypeptide)

↓
cleavage (several steps)

↓
active hormone - glucagon

↓
storage in cytosolic granules

↓
**secretion:** exocytosis (after stimulation)
Regulation of insulin and glucagon release from pancreatic cells

+ low blood glucose level
+ epinephrine (stress, trauma, severe exercise)
- regardless blood glucose level

+ high blood glucose level

Changes in blood levels after ingestion of carbohydrate-rich meal
**Mechanism of action**

**insulin:** tyrosine kinase system

1. Insulin binding activates receptor tyrosine kinase activity in the intracellular domain of the β-subunit of the insulin receptor.
2. Tyrosine residues of the β-subunit are auto-phosphorylated.
3. Receptor tyrosine kinase phosphorylates other proteins, for example, insulin receptor substrates (IRSs).
4. Phosphorylated IRS promotes activation of other protein kinases and phosphatases, leading to biologic action of insulin.

**Biologic effects of insulin:**
- Glucose uptake
- Glycogen synthesis
- Protein synthesis
- Fat synthesis
- Gluconeogenesis
- Glycogenolysis
- Lipolysis
- Altered gene expression

**Dephosphorylation of key enzymes**

↓ blood glucose level

**glucagon:** adenylate cyclase system

- Activation of multiple signaling pathways

**Phosphorylation of key enzymes**

↑ blood glucose level
Key regulatory enzymes in carbohydrate and lipid metabolism

**insulin**
dephosphorylated state

1. glycogen synthase
   $\text{UDPG} \rightarrow \text{glycogen}$

2. glycogen phosphorylase
   $\text{glycogen} \rightarrow \text{glucose-1-P}$

3. phosphofructokinase-2/fructose bisphosphate phosphatase-2
   fructose-2,6-bisphosphate $\rightarrow$ fructose-6-phosphate

4. pyruvate kinase
   phosphoenolpyruvate $\rightarrow$ pyruvate

5. pyruvate dehydrogenase
   pyruvate $\rightarrow$ acetyl-CoA

6. acetyl-CoA carboxylase
   acetyl-CoA $\rightarrow$ malonyl-CoA

7. hormone-sensitive lipase
   TAG $\rightarrow$ glycerol + MK

8. lipoprotein lipase
   TAG (VLDL, chylomicrones) $\rightarrow$ glycerol + FFA

9. HMG-CoA reductase
   HMG-CoA $\rightarrow$ mevalonate

**glucagon**
phosphorylated state

- glycogen synthase
- glycogen phosphorylase
+ phosphofructokinase-2/fructose bisphosphate phosphatase-2
+ pyruvate kinase
- pyruvate dehydrogenase
- acetyl-CoA carboxylase
+ hormone-sensitive lipase
- lipoprotein lipase
- HMG-CoA reductase

**Enzymes which are active in their dephosphorylated state**

- Glycogen phosphorylase
- Phosphofructokinase-2
- Hormone-sensitive lipase
- Lipoprotein lipase
- HMG-CoA reductase

**Enzymes which are inactive in their dephosphorylated state**

- Glycogen synthase
- Pyruvate dehydrogenase
- Acetyl-CoA carboxylase
- Hormone-sensitive lipase
- Lipoprotein lipase
- HMG-CoA reductase
Role of insulin in glucose transport into cells

- Insulin-dependent (-sensitive) tissues: namely muscle, adipose tissue
- Insulin-independent (-insensitive) tissues

**Membrane glucose transporter**

**Table**

<table>
<thead>
<tr>
<th>Active transport</th>
<th>Facilitated transport</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-sensitive</td>
<td>Most tissues (for example, skeletal muscle and adipose tissue)</td>
</tr>
<tr>
<td>Insulin-insensitive</td>
<td>Epithelia of intestine, renal tubules, choroid plexus</td>
</tr>
</tbody>
</table>

**Insulin** promotes **translocation** of insulin-sensitive glucose **transporters** (GLUT-4) from intracellular pool located in cytosolic vesicles to cell membrane → **↑ number of glucose transporters** in the cell membrane → **↑ glucose entry into cells**
### Glucose transporters

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Tissue Distribution</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUT 1</td>
<td>Red blood cells, brain microvessels (blood-brain barrier), kidney, colon, other cells</td>
<td>Low (K_m) ~ 1 mM, <em>ubiquitous</em> basal transporter</td>
</tr>
<tr>
<td>GLUT 2</td>
<td>Liver, pancreatic β-cells, basolateral surface of small intestine</td>
<td>High capacity, <em>low affinity</em> (K_m) ≥ 15 mM</td>
</tr>
<tr>
<td>GLUT 3</td>
<td>Neurons, placenta, testes</td>
<td>Low (K_m) ~ 1 mM, provide <em>glucose for cells metabolically dependent</em> on glucose</td>
</tr>
<tr>
<td>GLUT 4</td>
<td>Adipose tissue, skeletal muscle, heart</td>
<td>(K_m) ~ 5 mM, mediates <em>insulin-stimulated glucose uptake</em></td>
</tr>
<tr>
<td>GLUT 5</td>
<td>Small intestine, testes, sperm, (kidney, skeletal muscle, adipose tissue, brain – low levels)</td>
<td>Fructose transporter</td>
</tr>
</tbody>
</table>
Metabolic intertissue relations in well-fed (= absorptive) state
2-4 h after meal, ↑ insulin blood level

1. ↑ Blood glucose, amino acids, ↓ TAG (chylomicrons)
2. ↑ Insulin secretion, drop of glucagon
3. ↑ Synthesis of glycogen, TAG, proteins in tissues

Glucose = fuel for most tissues

Enzyme changes – most enzymes *dephosphorylated*:
1. Phosphofructokinase -2 + ↑ *glycolysis*
2. Glycogen synthase + ↑ *glycogen synthesis*
3. Acetyl-CoA carboxylase + ↑ *FA synthesis → lipogenesis*
Metabolic intertissue relations during starvation

Diet (weight reduction), inability to obtain food, trauma, surgery, burns, neoplasm..

↑ glucagon blood level

1. ↓ Blood glucose, amino, acids, TAG
2. ↑ Glucagon, ↓ insulin
3. Degradation of TAG, glycogen, proteins in tissues

Fatty acids and ketone bodies = fuel for most tissues
Glucose = fuel for brain and glucose-requiring tissues

Enzyme changes – most enzymes phosphorylated:
1. F-biP phosphatase-2 +
   ↑ gluconeogenesis
2. Glycogen phosphorylase +
   ↑ glycogenolysis
3. Hormone-sensitive lipase +
   ↑ lipolysis and ketogenesis

Processes that maintain glucose level mobilize fat stores
Overview of tissue metabolism during feed/fast cycle

**Well-fed state**
- Glucose, amino acids and fatty acids in the intestine
  - leads to Glucose, amino acids in portal vein
  - leads to Release of insulin by β cells of pancreas
  - leads to Release of glucagon by α cells of pancreas
  - leads to Synthesis of triacylglycerols
  - Glucose uptake
  - Glycogen synthesis
  - Fatty acid synthesis
  - Triglyceride synthesis
  - VLDL synthesis
  - Glucose uptake
  - Glycogen synthesis
  - Protein synthesis

**Tissues involved**
- Intestine and portal vein
- Pancreas
- Adipose
- Liver
- Muscle
- Brain

**Starvation**
- No nutrients in the intestine
  - leads to Glucose, amino acids in blood
  - leads to Release of insulin by β cells of pancreas
  - leads to Release of glucagon by α cells of pancreas
  - leads to Release of fatty acids produced by hydrolysis of triacylglycerol
  - leads to Release of glucose produced by glycogen degradation
  - leads to Release of glucose produced by gluconeogenesis
  - leads to Release of ketones
  - leads to Fatty acid and ketone body use
  - leads to Release of amino acids
  - leads to Glucose and ketones completely oxidized to CO₂ and water
  - leads to Glucose for brain and other glucose-requiring tissues
  - leads to Fatty acids and ketones as fuels for non-glucose-requiring tissues

**Capture of energy as glycogen and triacylglycerols, and replenishment of any protein degraded during previous post-absorptive period**
# Diabetes mellitus

**Characteristics:** elevated (fasting) blood glucose level

- **Type 1** = insulin-dependent diabetes mellitus (IDDM)  
  absolute deficiency of insulin (destruction of pancreatic β-cells)

- **Type 2** = non-insulin-dependent diabetes mellitus (NIDDM)  
  relative deficiency of insulin - synthesis of abnormal insulin  
  - decreased secretion of insulin  
  - insulin resistance in peripheral tissues

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE OF ONSET</strong></td>
<td>Usually during childhood or puberty; symptoms develop rapidly</td>
<td>Frequently after age 35; symptoms develop gradually</td>
</tr>
<tr>
<td><strong>NUTRITIONAL STATUS AT TIME OF DISEASE ONSET</strong></td>
<td>Frequently undernourished</td>
<td>Obesity usually present</td>
</tr>
<tr>
<td><strong>PREVALENCE</strong></td>
<td>900,000 = 10% of diagnosed diabetics</td>
<td>10 Million = 90% of diagnosed diabetics</td>
</tr>
<tr>
<td><strong>GENETIC PREDISPOSITION</strong></td>
<td>Moderate</td>
<td>Very strong</td>
</tr>
<tr>
<td><strong>DEFECT OR DEFICIENCY</strong></td>
<td>β Cells are destroyed, eliminating production of insulin</td>
<td>Insulin resistance combined with inability of β cells to produce appropriate quantities of insulin</td>
</tr>
<tr>
<td><strong>FREQUENCY OF KETOSIS</strong></td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>PLASMA INSULIN</strong></td>
<td>Low to absent</td>
<td>High early in disease; low in disease of long duration</td>
</tr>
<tr>
<td><strong>ACUTE COMPLICATIONS</strong></td>
<td>Ketoacidosis</td>
<td>Hyperosmolar coma</td>
</tr>
<tr>
<td><strong>TREATMENT WITH ORAL HYPOGLYCEMIC DRUGS</strong></td>
<td>Unresponsive</td>
<td>Responsive</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td>Insulin is always necessary</td>
<td>Diet, exercise, oral hypoglycemic drugs, +/- insulin</td>
</tr>
</tbody>
</table>
Metabolic changes in type 1 diabetes
↓ insulin, ↑ glucagon (secretion is not inhibited by insulin)

1. ↓ Glucose uptake in muscle and adipose tissue → hyperglycemia, glucosuria

2. ↑ Gluconeogenesis in liver (phosphorylated = activated F-biP phosphatase-2)

3. ↑ Lipolysis in adipocytes → fatty acids → liver → ↑ β-oxidation → ↑ ketogenesis (high production of acetyl-CoA) → ketosis (ketoacidosis, ketonuria) → ↑ TAG (VLDL) synthesis in liver (increased fatty acid delivery)

4. ↓ Activity of lipoprotein lipase → ↓ chylomicron and VLDL degradation → ↓ hypertriacylglycerolemia

Treatment:
insulin ⇒ decrease of glycemia ⇒ inhibition of long-term complications of diabetes

Complications: insulin overdosage ⇒ hypoglycemia ⇒ coma
development of deficiency in glucagon secretion, impairment in epinephrine secretion after 3-4 years
Type 2 diabetes - non-insulin-dependent diabetes mellitus NIDDM

- 80-90% of diabetic patients
- Obese patients
- Dysfunction of β-cells
- Insulin resistance ↓
  - Dysfunction/lack of insulin receptors (down-regulation),
- Abnormal insulin

hyperglycemia ⇒ glycosuria
Ketoacidosis, ketonuria – rare!

Treatment:
- Diet, antidiabetic drugs, exercise
- Insulin not required (namely at the beginning of treatment)
- Response only in patients with decreased insulin secretion
Metabolic changes in type 2 diabetes

1. **↓ Glucose uptake** in muscle and adipose tissue

2. **Uncontrolled production of glucose** in liver (glycogen phosphorylase, F-biP phosphatase phosphorylated = activated)

   ![hyperglycemia, glucosuria]

3. **Lipolysis** in adipose tissue:
   - ![normal](not increased)
Chronic complications of diabetes

- a major cause of morbidity and mortality in diabetic patients

Acute and chronic hyperglycemia

1. ↑ Intracellular glucose + its metabolites
   → sorbitol (eye) → cataracts

2. Glycation of proteins (altered function)
   e.g. collagen, elastin → microvascular changes
   → development of macrovascular diseases
   premature atherosclerosis, retinopathy, nephropathy, neuropathy
Protein glycation

Nonenzymic process – slow reaction = condensation of glucose with the certain reactive amino groups on the proteins – formation of labile Schiff base → rearrangement to stable ketoamine (=fructosamine form)

Hb – small fraction glycated (N-terminal valine of β-chains) throughout the 120-day life span of erythrocytes → glycated hemoglobin HbA₁c

enhanced levels in diabetic individuals → monitoring the effects of a diet or therapy over period of 2-3 months

Glycated albumin (=fructosamine) -reflects integrated plasma glucose levels over a shorter period (2-3 weeks) – half-life of albumin = 19 days
Correlation between mean blood level and HbA$_{1C}$ in patients with type 1 diabetes

Relationship of HbA$_{1C}$ control and diabetic retinopathy

![Typical mean blood glucose concentrations observed in insulin-dependent diabetics treated with:]

Normal mean [glucose] in non-diabetic individuals
Mean [glucose] in patients treated with intensive insulin therapy
Mean [glucose] in patients treated with standard insulin therapy

Percent Hemoglobin A$_{1C}$

Mean blood [glucose], mg/dl

5.6 8.3 12.7 mmol/l

![The benefits of an improvement in glycemic control occurred over the entire range of HbA$_{1C}$ values; thus, any improvement in glycemic control is beneficial.]

Mean HbA$_{1C}$ = 11%

Prevalence of retinopathy (%)

Length of follow-up, years

8% 7% 8% 10% 9%
Advanced glycation end-products (AGEs)

Formed due to accelerated chemical modification of plasma proteins by glucose during long-term hyperglycemia

Level of plasma AGEs - correlates with diabetic complications - marker of later developments of vascular complications (atherosclerosis)

AGEs inhibitors are investigated as drug candidates for the treatment of diabetic complications in tissues

Structures of some important AGEs mostly Lys, Arg residues modified