The integrated endocrine control of metabolism. Starvation, stress and general adaptation syndrome.

Long-term regulation of food intake and body weight.

Lo. 76.

Katecholamines:
adrenalin (adrenal medulla) - noradrenalin (sympathetic terminals)

Mobilization of reserves

Activation by: hypoglycemia, workload (fight or flight), trauma etc.

Effects:

Liver: glycogenolysis: $\alpha_1$ receptor - Ca $^2+$ - calmodulin - phosphorilase-kinase

$\beta_2$ receptor - cAMP

increased gluconeogenesis

adipocytes: lipolysis: $\beta_3$-receptors (hormone-sensitive lipase)

muscle: permissive (direct effectors: motor nerves)

pancreas: augments glucagon release
Metabolic effects of glucocorticoids (cortisol and cortisone):

Liver – anabolism;
Glycogen synthesis↑ and gluconeogenesis↑
Protein (plasma) synthesis↑

Muscle and adipocytes –catabolism (proteolytic and ketogenic effect)
Decrease in the expression of GLUT-4 transporter

localisation-dependent actions on the lipid metabolism:
- limbs: lipid mobilisation (permissive actions on B3 receptors)
- Trunk, neck, face: adipocyte proliferation

de proteolysis↑ (skin, bones)

Permissive actions: glucagon- and adrenergic-receptors

General Adaptation Syndrome (GAS) induced by physical stressors

Growth hormone (GH)

 oversecretion: seconder (hypophyser) diabetes mellitus

Metabolits affecting GH release:

- Hypoglycaemia, amino acids (pl. arginin): stimulants
- FFA inhibits

Metabolic effects of GH:

High cc.: decreases the insulin sensitivity of peripehral tissues
Enhanced lypolysis - ketogenic action
gluconeogenesis↑, but: protein breakdown is inhibited in the muscles
### Major effects of metabolic hormones controlling the overall flow of fuels

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Liver</th>
<th>Muscle</th>
<th>Adipose tiss.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>+ glycogenesis</td>
<td>- amino acid uptake</td>
<td>+ lipolysis</td>
</tr>
<tr>
<td></td>
<td>+ gluconeogenesis</td>
<td>+ proteolysis</td>
<td>- insulin action</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- insulin action</td>
<td></td>
</tr>
<tr>
<td>Growth hormone</td>
<td>+ gluconeogenesis</td>
<td>+ amino acid uptake</td>
<td>+ lipolysis</td>
</tr>
<tr>
<td></td>
<td>+ IGFs/IGFBP</td>
<td>- glucose uptake</td>
<td>- glucose uptake</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+ glycogenolysis</td>
<td>+ glycogenolysis</td>
<td>+ lipolysis</td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td>+ gluconeogenesis</td>
<td>+ proteolysis</td>
<td>+ lipolysis</td>
</tr>
<tr>
<td></td>
<td>+ ketogenesis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* + stimulates  
  - inhibits

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### (Patho)physiology of fasting and starvation

Early phase of fasting: low insulin/high glucagon levels  
Glycogen break down (depletion) + gluconeogenesis

Prolonged fasting, onset of starvation:  
Priorities: keep sufficient glucose level – preserve proteins

Hydrolysis of TGs elevates (feeding muscles, liver)  
Reduction in the protein degradation (saving)  
Reduction in the metabolic rate  
Ketogenesis (ketosis) – from 3rd day neurons and cardiomyocytes start to utilize KBs

Survival is determined by the amount of fat stores (1-3 months)  
Terminal phase:  
Exhaustion of fat reserves  
Mobilisation of proteins – loss of function, death
Brain starts to use KBs

Table 30.2 Fuel metabolism in starvation

<table>
<thead>
<tr>
<th>Fuel exchanges and consumption</th>
<th>Amount formed or consumed in 24 hours (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3d day</td>
</tr>
<tr>
<td>Fuel use by the brain</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>100</td>
</tr>
<tr>
<td>Ketone bodies</td>
<td>50</td>
</tr>
<tr>
<td>All other use of glucose</td>
<td>50</td>
</tr>
<tr>
<td>Fuel mobilization</td>
<td></td>
</tr>
<tr>
<td>Adipose-tissue lipolysis</td>
<td>180</td>
</tr>
<tr>
<td>Muscle-protein degradation</td>
<td>75</td>
</tr>
<tr>
<td>Fuel output of the liver</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>150</td>
</tr>
<tr>
<td>Ketone bodies</td>
<td>150</td>
</tr>
</tbody>
</table>
Flow chart of energy substrate flow during the chronic phase of starvation

Numbers indicate the estimated substrate flow (g/h)

Determination of the ideal body mass

**BMI = Body Mass Index** (Quetelet index):

body weight (kg)/(body high in meter)$^2$

normal range: 19-25

The ideal body composition (% of the body weight):

- extra cellular fluid volume: 15%
- total fat content: 20%
- total muscle content: 40%

Complications of obesity

- Cerebrovascular disease (+53%)
- Coronary heart disease (+35%)
- Respiratory disease
- Gallstones
- Hernias
- Arthritis
- Varicose veins

- Diabetes mellitus (+133%)
- Hypertension
- Accidents (+18%)
- Cancer (+16%)
Waist circumference >102 cm
Serum triglycerides↑
HDL↓
Blood pressure > 130/85 mmHg
FBG>7.1 mM

The phenotype of “survival” genes in an environment of plenitude

Note: Prevalence data is among adult US population from 2000 resists (146 million)
Sources:
(3) "The Continuing Epidemic of Obesity and Diabetes in the United States," JAMA, September 13, 2001 - Vol. 286, No. 11.

Leptin (ob/ob) and leptin receptor (db/db) deficient mice: obesity, hyperphagia, hypoactivity – genetic models of obesity

ob/ob mutant (leptin deficient)   „wild type”
**Leptin (leptos – thin)**

The first hormone originating from adipose tissue
Related to cytokines – acts on cytokine-like receptors

Secretion rate and plasma concentration reflects the amount of adipose tissue (mostly subcutaneous)

Acts on hypothalamic neurons – n. arcuatus – anorexigenic effects

Increases the energy expenditure/metabolic rate

Glucocorticoids, inflammatory cytokines inhibit the leptin synthesis

**Adiponectin**

Synthesized in the fat tissue
Structurally related to complement factors (different multimer complexes)
Plasma concentration is inversely proportional with the size of adipose tissue
Experimental diabetes – improvement of the glycaemic control (increased insulin sensitivity) – muscle and adipose tissue glucose uptake (AMP-kinase pathway)

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**Feed-back regulation to control the amount of stored fat and body weight**

- **Default behavior**
  - Food intake
  - Energy expenditure
  - Hypothalamus

- **Other adipokines:**
  - TNF-α, IL-6 (Insulin-resistance)
  - Adiponectin (BMR↑)

- **High leptin**
  - Positive balance
    - High fat diet

- **Low leptin**
  - Negative balance
    - Food depletion

- **No leptin**
  - Extremely negative balance
    - Genetic leptin null

- **ob/ob**
Resistin (structural similarity with adiponectin)  
Adipocyte + tissue macrophages  
Decreases insulin sensitivity  
Action is antagonized by OADs (risoglitason)