Integration and Hormonal Regulation of Mammalian Metabolism

Lehninger 3rd ed. Chapters 23
Citric acid cycle: acetyl-CoA $\rightarrow$ 2CO$_2$

Oxidative phosphorylation: ATP synthesis

Carbohydrate catabolism
- Glycogenolysis: glycogen $\rightarrow$ glucose 1-phosphate $\rightarrow$ blood glucose
- Hexose entry into glycolysis: fructose, mannose, galactose $\rightarrow$ glucose 6-phosphate
- Glycolysis: glucose $\rightarrow$ pyruvate
- Pyruvate dehydrogenase reaction: pyruvate $\rightarrow$ acetyl-CoA
- Lactic acid fermentation: glycogen $\rightarrow$ lactate + 2ATP
- Pentose phosphate pathway: glucose 6-phosphate $\rightarrow$ pentose phosphates + NADPH

Carbohydrate anabolism
- Gluconeogenesis: citric acid cycle intermediates $\rightarrow$ glucose
- Glucose-alanine cycle: glucose $\rightarrow$ pyruvate $\rightarrow$ alanine $\rightarrow$ glucose
- Glycogen synthesis: glucose 6-phosphate $\rightarrow$ glucose 1-phosphate $\rightarrow$ glycogen

Amino acid and nucleotide metabolism
- Amino acid degradation: amino acids $\rightarrow$ acetyl-CoA, citric acid cycle intermediates
- Amino acid synthesis
- Urea cycle: NH$_3$ $\rightarrow$ urea
- Glucose-alanine cycle: alanine $\rightarrow$ glucose
- Nucleotide synthesis: amino acids $\rightarrow$ purines, pyrimidines
- Hormone and neurotransmitter synthesis

Fat catabolism
- $\beta$ Oxidation of fatty acids: fatty acid $\rightarrow$ acetyl-CoA
- Oxidation of ketone bodies: $\beta$-hydroxybutyrate $\rightarrow$ acetyl-CoA $\rightarrow$ CO$_2$

Fat anabolism
- Fatty acid synthesis: acetyl-CoA $\rightarrow$ fatty acids
- Triacylglycerol synthesis: acetyl-CoA $\rightarrow$ fatty acids $\rightarrow$ triacylglycerol
- Ketone body formation: acetyl-CoA $\rightarrow$ acetoacetate, $\beta$-hydroxybutyrate
- Cholesterol and cholesteryl ester synthesis: acetyl-CoA $\rightarrow$ cholesterol $\rightarrow$ cholesteryl esters
- Phospholipid synthesis: fatty acids $\rightarrow$ phospholipids
Sugar pathways

Glucose 6-phosphate in the liver

Liver glycogen → Blood glucose

Glycolysis

Pentose phosphate pathway → NADPH

Triacylglycerols, phospholipids

Fatty acids, cholesterol

Pyruvate

Ribose 5-phosphate

Acetyl-CoA

Citric acid cycle

Oxidative phosphorylation

ADP + Pi → ATP

O2 + H2O → e−

CO2
Amino acids
Lipids

Transport of acetyl groups

Liver lipids

Fatty acids in the liver

Plasma lipoproteins

Free fatty acids in blood

β oxidation

Steroid hormones

Bile salts

Cholesterol

Acetyl-CoA

Ketone bodies in blood

NADH

Citric acid cycle

CO₂

O₂

H₂O

ADP + Pᵢ

ATP

Oxidative phosphorylation
During recovery

\[ \text{ATP} + \text{Creatine} \rightarrow \text{Phosphocreatine} \]

Creatine kinase

During Activity
Muscle: ATP produced by glycolysis for rapid contraction.

Liver: ATP used in synthesis of glucose (gluconeogenesis) during recovery.
Starvation

Ketone bodies

Normal diet

Glucose

CO₂

ADP + P₁

ATP

Electrogenic transport by Na⁺K⁺ ATPase
Rested (a)

Sleep (b) deprived

12.00  2.00
mg/100g/min
Glucose
Inorganic components (10%)
NaCl, bicarbonate, phosphate, CaCl₂, MgCl₂, KCl, Na₂SO₄

Organic metabolites and waste products (20%)
glucose, amino acids, lactate, pyruvate, ketone bodies, citrate, urea, uric acid

Plasma proteins (70%)
Major plasma proteins: serum albumin, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL), immunoglobulins (hundreds of kinds), fibrinogen, prothrombin, many specialized transport proteins such as transferrin
Blood glucose (mg/100 mL)

100 —
90 —
80 —
70 —
60 —
50 —
40 —
30 —
20 —
10 —
0 —

Normal range

Subtle neurological signs; hunger
Release of glucagon, epinephrine, cortisol
Sweating, trembling

Lethargy
Convulsions, coma

Permanent brain damage (if prolonged)
Death
How does the blood glucose level remain constant?

A tale of 3 hormones:
1. Insulin.
2. Glucagon.
3. Epinephrine.

and three tissues:
1. Blood.
2. Liver.
3. Adipose tissue.
### Physiological and Metabolic Effects of Epinephrine: Preparation for Action

<table>
<thead>
<tr>
<th>Physiological</th>
<th>Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Heart rate</td>
<td>Increased delivery of $O_2$ to tissues (muscle)</td>
</tr>
<tr>
<td>↑ Blood pressure</td>
<td>Increased production of glucose for fuel</td>
</tr>
<tr>
<td>↑ Dilation of respiratory passages</td>
<td>Increased ATP production in muscle</td>
</tr>
<tr>
<td></td>
<td>Increased availability of fatty acids as fuel</td>
</tr>
<tr>
<td></td>
<td>Reinforce metabolic effects of epinephrine</td>
</tr>
</tbody>
</table>

- ↑ Glycogen breakdown (muscle, liver)
- ↓ Glycogen synthesis (muscle, liver)
- ↑ Gluconeogenesis (liver)
- ↑ Glycolysis (muscle)
- ↑ Fatty acid mobilization (adipose tissue)
- ↑ Glucagon secretion
- ↓ Insulin secretion
Glucagon

Insulin

**Muscle:**
Insulin stimulates glucose uptake and consumption

**Liver:**
Glucagon stimulates glucose synthesis and export
<table>
<thead>
<tr>
<th>Metabolic effect</th>
<th>Effect on glucose metabolism</th>
<th>Target enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Glycogen breakdown (liver)</td>
<td>Glycogen → glucose</td>
<td>↑ Glycogen phosphorylase</td>
</tr>
<tr>
<td>↓ Glycogen synthesis (liver)</td>
<td>Less glucose stored as glycogen</td>
<td>↓ Glycogen synthase</td>
</tr>
<tr>
<td>↓ Glycolysis (liver)</td>
<td>Less glucose used as fuel in liver</td>
<td>↓ Phosphofructokinase-1</td>
</tr>
<tr>
<td>↑ Gluconeogenesis (liver)</td>
<td>Amino acids</td>
<td>↑ Fructose 1,6-bisphosphatase</td>
</tr>
<tr>
<td></td>
<td>Glycerol</td>
<td>↓ Pyruvate kinase</td>
</tr>
<tr>
<td></td>
<td>Oxaloacetate</td>
<td></td>
</tr>
<tr>
<td>↑ Fatty acid mobilization (adipose tissue)</td>
<td>Less glucose used as fuel by liver, muscle</td>
<td>↑ Triacylglycerol lipase</td>
</tr>
</tbody>
</table>
### Table 23-4

**Available Metabolic Fuels in a Normal 70 kg Man and in an Obese 140 kg Man at the Beginning of a Fast**

<table>
<thead>
<tr>
<th>Type of fuel</th>
<th>Weight (kg)</th>
<th>Caloric equivalent [thousands of kcal (kJ)]</th>
<th>Estimated survival (months)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal 70 kg man:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triacylglycerols (adipose tissue)</td>
<td>15</td>
<td>141 (589)</td>
<td></td>
</tr>
<tr>
<td>Proteins (mainly muscle)</td>
<td>6</td>
<td>24 (100)</td>
<td></td>
</tr>
<tr>
<td>Glycogen (muscle, liver)</td>
<td>0.225</td>
<td>0.90 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Circulating fuels (glucose, fatty acids,</td>
<td>0.023</td>
<td>0.10 (0.42)</td>
<td></td>
</tr>
<tr>
<td>triacylglycerols, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>166 (694)</td>
<td>3</td>
</tr>
<tr>
<td><strong>Obese 140 kg man:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triacylglycerols (adipose tissue)</td>
<td>80</td>
<td>752 (3,140)</td>
<td></td>
</tr>
<tr>
<td>Proteins (mainly muscle)</td>
<td>8</td>
<td>32 (134)</td>
<td></td>
</tr>
<tr>
<td>Glycogen (muscle, liver)</td>
<td>0.23</td>
<td>0.92 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Circulating fuels</td>
<td>0.025</td>
<td>0.11 (0.46)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>785 (3,280)</td>
<td>14</td>
</tr>
</tbody>
</table>

*Survival time is calculated on the assumption of a basal energy expenditure of 1,800 kcal/day.*
A starving liver

1. Protein degradation yields glucogenic amino acids.
2. Urea is exported to the kidney and excreted in urine.
3. Citric acid cycle intermediates are diverted to gluconeogenesis.
4. Glucose is exported to the brain via the bloodstream.
5. Fatty acids (imported from adipose tissue) are oxidized as fuel, producing acetyl-CoA.
6. Lack of oxaloacetate prevents acetyl-CoA entry into the citric acid cycle; acetyl-CoA accumulates.
7. Acetyl-CoA accumulation favors ketone body synthesis.
8. Ketone bodies are exported via the bloodstream to the brain, which uses them as fuel.

Protein → Amino acids → Urea → NH₃ → Urea

Glucose 6-phosphate → P₁ → Glucose → Fatty acids

Oxaloacetate → Citrate → Hepatocyte

Acetoacetyl-CoA → Ketone bodies
### Table 23-5

**Effect of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen**

<table>
<thead>
<tr>
<th>Metabolic effect</th>
<th>Target enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Glucose uptake (muscle)</td>
<td>↑ Glucose transporter</td>
</tr>
<tr>
<td>↑ Glucose uptake (liver)</td>
<td>↑ Glucokinase</td>
</tr>
<tr>
<td>↑ Glycogen synthesis (liver, muscle)</td>
<td>↑ Glycogen synthase</td>
</tr>
<tr>
<td>↓ Glycogen breakdown (liver, muscle)</td>
<td>↓ Glycogen phosphorylase</td>
</tr>
<tr>
<td>↑ Glycolysis, acetyl-CoA production (liver, muscle)</td>
<td>↑ Phosphofructokinase-1</td>
</tr>
<tr>
<td>↑ Fatty acid synthesis (liver)</td>
<td>↑ Pyruvate dehydrogenase complex</td>
</tr>
<tr>
<td>↑ Triacylglycerol synthesis (adipose tissue)</td>
<td>↑ Acetyl-CoA carboxylase</td>
</tr>
<tr>
<td></td>
<td>↑ Lipoprotein lipase</td>
</tr>
</tbody>
</table>
The neuroendocrine system
Thyrotropin-releasing hormone:
1 million pigs.
2 million sheep
20 tons of hypothalami

Pyroglutamate   Histidine   Prolylamide
pyroGlu-His-Pro-NH₂
(b)
Peptide or amine hormone binds to receptor on the outside of the cell; acts through receptor without entering the cell.

Steroid or thyroid hormone enters the cell; hormone-receptor complex acts in the nucleus.

- **Plasma membrane**
  - Second messenger (e.g., cAMP)
    - Altered activity of preexisting enzyme
    - Altered amount of newly synthesized proteins
  - Altered transcription of specific genes
    - Nucleus
<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
<th>Parent /origin</th>
<th>Synthetic path</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptide</td>
<td>Leu-enkephalin</td>
<td>Tyr–Gly–Gly–Phe–Leu</td>
<td>Proteolytic processing of proenzyme</td>
<td>Plasma membrane receptors; second messengers</td>
</tr>
<tr>
<td>Catecholamine</td>
<td>Epinephrine</td>
<td>Tyrosine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eicosanoid</td>
<td>PGE&lt;sub&gt;1&lt;/sub&gt;</td>
<td>20:4 Fatty acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td>Testosterone</td>
<td>Cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinoid</td>
<td>Retinoic acid</td>
<td>Vitamin A</td>
<td></td>
<td>Nuclear receptors; transcriptional regulation</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Triiodothyronine (T&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>Tyr in thyroglobulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>1,25-dihydroxycholecalciferol</td>
<td>Cholesterol or vitamin D</td>
<td></td>
<td>Cytosolic receptor (guanylate cyclase) and second messenger (cGMP)</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Nitric oxide</td>
<td>NO&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Arginine + O&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
</tr>
</tbody>
</table>
Tyrosine

$\rightarrow$

L-DOPA

$\rightarrow$

Dopamine

$\rightarrow$

Norepinephrine

$\rightarrow$

Epinephrine
Phospholipids

→

Arachidonate

(20 : 4)

→

Prostaglandins
Thromboxanes
Leukotrienes
Cholesterol → Progesterone →
- Cortisol (glucocorticoid)
- Aldosterone (mineralocorticoid)
- Testosterone
  - Estradiol (sex hormones)
7-Dehydrocholesterol

→ UV light

Vitamin D₃
(cholecalciferol)

→

25-Hydroxycholecalciferol

→

1,25-Dihydroxycholecalciferol
β-Carotene

→

Vitamin A₁
(retinol)

→

Retinoic acid
Thyroglobulin–Tyr

\[ \rightarrow \]

Thyroglobulin–Tyr–I

(iodinated Tyr residues)

\[ \rightarrow \]

proteolysis

\[ \rightarrow \]

Thyroxine \( (T_4) \)

and

triiodothyronine \( (T_3) \)
Regulating regulators

Sensory input from environment

Central nervous system

Hypothalamus

Hypothalamic hormones
(releasing factors)

Anterior pituitary

Posterior pituitary

First targets

Corticotropin (ACTH)
$M_r 4,500$

Thyrotropin
$M_r 28,000$

Follicle-stimulating hormone
$M_r 24,000$

Luteinizing hormone
$M_r 20,500$

Somatotropin (growth hormone)
$M_r 21,500$

Prolactin
$M_r 22,000$

Oxytocin
$M_r 1,007$

Vasopressin (antidiuretic hormone)
$M_r 1,040$

Blood glucose level

Second targets

Adrenal cortex

Thyroid

Ovaries/testes

Cortisol, corticosterone, aldosterone

Thyroxine ($T_4$), triiodothyronine ($T_3$)

Progesterone, estradiol

Testosterone

Ultimate targets

Many tissues

Muscles, liver

Reproductive organs

Liver, bone

Mammary glands

Smooth muscle, mammary glands

Arterioles

Liver, muscles

Liver, muscles, heart
Afferent nerve signals to hypothalamus

Hypothalamus

Nerve axons

Release of hypothalamic factors into arterial blood

Anterior pituitary

Capillary network

Release of anterior pituitary hormones (tropins)

Posterior pituitary

Release of posterior pituitary hormones (vasopressin, oxytocin)

Veins carry hormones to systemic blood

(a)

(b)
Hypothalamus regulation of food intake and energy expenditure