Endocrine Glands and the General Principles of Hormone Action

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“Classical” Endocrine Glands
A more complete listing of the endocrine glands

<table>
<thead>
<tr>
<th>Endocrine gland</th>
<th>Major hormones</th>
<th>Primary target organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose tissue</td>
<td>Leptin</td>
<td>hypothalamus</td>
</tr>
<tr>
<td>Adrenal cortex</td>
<td>Glucocorticoids</td>
<td>liver, muscle</td>
</tr>
<tr>
<td></td>
<td>Aldosterone</td>
<td>kidneys</td>
</tr>
<tr>
<td>Adrenal medulla</td>
<td>Epinephrine</td>
<td>heart, blood vessels</td>
</tr>
<tr>
<td>Heart</td>
<td>Atrial natriuretic hormones</td>
<td>kidneys</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>Releasing and inhibiting hormones</td>
<td>pituitary</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Secretin, cholecystokinin</td>
<td>stomach, liver, pancreas</td>
</tr>
<tr>
<td>Islets of Langerhans</td>
<td>Insulin</td>
<td>fat, muscle, brain</td>
</tr>
<tr>
<td></td>
<td>glucagon</td>
<td>liver, fat</td>
</tr>
<tr>
<td></td>
<td>erythropoietin</td>
<td>bone marrow</td>
</tr>
<tr>
<td>Liver</td>
<td>Somatomedins</td>
<td>cartilage</td>
</tr>
<tr>
<td>Ovaries</td>
<td>estradiol, progesterone</td>
<td>repro. tract, mammary glands</td>
</tr>
<tr>
<td>Parathyroid glands</td>
<td>Parathyroid hormone</td>
<td>bone, small intestine, kidneys</td>
</tr>
<tr>
<td>Pineal gland</td>
<td>Melatonin</td>
<td>hypothalamus, ant. Pituitary endocrine glands</td>
</tr>
<tr>
<td>Pituitary, anterior</td>
<td>Trophic hormones</td>
<td>kidney, blood vessels</td>
</tr>
<tr>
<td>Pituitary, posterior</td>
<td>Antidiuretic hormone</td>
<td>uterus, mammary glands</td>
</tr>
<tr>
<td></td>
<td>oxytocin</td>
<td>small intestine</td>
</tr>
<tr>
<td>Skin</td>
<td>1,25-dihydroxy vitamin D&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Stomach</td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastrin</td>
<td>prostate, seminal vesicles</td>
</tr>
<tr>
<td>Testes</td>
<td>Testosterone</td>
<td>lymph nodes</td>
</tr>
<tr>
<td>Thymus</td>
<td>Thymosin</td>
<td>Many</td>
</tr>
<tr>
<td>Throid gland</td>
<td>T3, T4, calcitonin</td>
<td></td>
</tr>
</tbody>
</table>
Exocrine and Endocrine Glands

Connecting cells persist to form duct

Deepest cells become secretory

Connecting cells disappear

Capillary

Deepest cells remain to secrete into capillaries

Paras
**Exocrine Glands and Endocrine glands**

**Exocrine Glands:** Secrete into a duct and to the outside of a body surface

**Examples:** sweat, tear, saliva

**Endocrine Glands:** Secrete (hormone) into the blood

Hormone circulates in blood and acts at target organs where hormone receptor is expressed

**Examples:** insulin

**Exocrine and Endocrine glands:**

<table>
<thead>
<tr>
<th>Exocrine</th>
<th>Endocrine</th>
<th>Exocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver:</td>
<td>IGF</td>
<td>Bile</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Pancreatic juice</td>
<td>insulin, glucagon, PP</td>
</tr>
</tbody>
</table>
Chemical Structure of Hormones

1. **Amines (amino acid derivatives)**
   - Tyrosine derived: epinephrine, thyroid hormones
   - Tryptophan derived: melatonin

2. **Polypeptides**
   - Insulin, leptin, ADH

3. **Glycoproteins**
   - FSH, LH

4. **Steroids (cholesterol derived)**
   - Glucocorticoids, testosterone, vitamin D
Mechanisms of Actions of Hormones

All hormones act by binding to their receptors

• Some receptors are located on the **cell surface**
  ▪ Polar hormones (insulin, leptin)

• Some receptors are located in the **cytoplasm**
  ▪ Lipophilic hormones (steroids, thyroid hormones)

• Some receptors are located in the **nucleus**
  ▪ Lipophilic hormones (TZDs, Fibrates)
Assay and Measurement of Hormones

Bioassay
Chemical assay
Radioimmunoassay (1977 Nobel prize)

Receptor binding assay (Scatchard plot)
Action of nuclear hormones

hPPARδ
(PPARγ, Nuc-1, FAAR)

hPPARα

hPPARγ₁

hPPARγ₂

Coactivators

Ligands

PPAR

RXR

AGGNCAXAGGNCA

TCCNGTXTCCNGT

Corepressors

Ligands
Actions of PPARγ, a nuclear hormone receptor

Adipose
- FA storage (FABP)
- FA oxidation (UCP3)

Muscle
- glucose oxidation (PDK4)
- FA oxidation (UCP3)

Liver
- gluconeogenesis (PEPCK)

Macrophage
- oxLDL uptake (CD36)
- CH efflux (LXRα and ABCA1)

FFA

insulin sensitization
glucose lowering
triglyceride lowering
antiatherosclerotic
antihypertensive
Regulation of hormone secretion: A simple feedback loop

↑ Blood glucose
↓
β cells in the pancreas
↓
↑ Insulin secretion
↓
↑ Uptake of blood glucose
↓ blood glucose

Liver
Muscle
Fat

Glucose
↓
Glycogen

Glucose
↓
Triglyceride
Structure of an islet
How glucose and therapeutic drugs cause insulin secretion
Two general principles of hormone action

Acts on cells containing the receptor

Action is regulated by a feedback mechanism
Overweight and NIDDM in the U.S.
Leptin: a new hormone from fat

- Made in the adipose tissues
- A polypeptide of 167 amino acids
- Product is secreted into blood
- Its receptor is found in many tissues
- Leptin deficiency causes obesity, infertility, and many other complications
Tissue distribution of leptin
Leptin gene mutation in *ob/ob* mouse

![Diagram of Leptin gene mutation in ob/ob mouse](attachment:diagram.png)

**Diagram Details**
- **R105 (CGA→TGA)**
- **167**
Leptin Receptor Isoforms

**Long**
- OB-Rb

**Short**
- OB-Ra
- OB-Rc
- OB-Rd

**Soluble**
- OB-Re
Tissue distribution of the leptin receptor

Heart
Brain
Spleen
Lung
Liver
Sk. Muscle
Kidney
Testis

Probe Length (kb)

Common 0.60
Ob-Ra 0.25
Ob-Rb 0.20
Actin 2.00
Rodent Mutations at the $db$ Locus

**Mouse**
- Ob-Rb
- C57BL/KsJ $db/db$
- $db^{3J}/db^{3J}$
- $db^{Pas}/db^{Pas}$

**Rat**
- $fa/fa$
- $fa^{k}/fa^{k}$

Extracellular | TMR | Intracellular

<table>
<thead>
<tr>
<th></th>
<th>Mouse</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ob-Rb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$db/db$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$db^{3J}/db^{3J}$</td>
<td>625</td>
<td></td>
</tr>
<tr>
<td>$db^{Pas}/db^{Pas}$</td>
<td>281</td>
<td></td>
</tr>
<tr>
<td>$fa/fa$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$fa^{k}/fa^{k}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- $Q269P$
Leptin Levels in Lean and Obese Rodents

$+/+$  $db/db$  $+/+$  $fa/fa$

Leptin western

Leptin northern

$\beta$-actin
Leptin levels in lean and ZDF rats
Soluble Leptin Receptor Levels in Lean and ZDF Rats

<table>
<thead>
<tr>
<th>Plasma (µl)</th>
<th>Lean</th>
<th>ZDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M.W. (kDa)

- 203
- 116

OB-Re
Jak-STAT Pathway of Leptin Receptor Signal Transduction

Leptin activates the Jak-STAT pathway by phosphorylating the Jak2 protein kinases associated with the Ob-Ra and Ob-Rb receptors. This leads to the phosphorylation of STAT3, which then moves to the nucleus.
Hypothalamic signaling pathways regulating energy homeostasis
Severe postnatal obesity of a child with leptin mutation
One example of human leptin mutation
Leptin treatment of a girl with leptin deficiency
SUMMARY

• Most tissues are endocrine glands and have the capacity to secrete molecules that act on other tissues
• All hormones act by interaction with their receptors
• The action of most hormones are regulated by a negative feedback mechanism