Functional Anatomy and Physiology of the Endocrine System

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Outline

• Basic hormonal physiology

• Overview of different hormonal axes
  o Posterior pituitary
  o Growth hormone
  o Thyroid hormone
  o Adrenal hormones
  o Gonadal hormones
What is Endocrinology?

• Study of hormones (and their gland of origin), their receptors, the intracellular signalling pathways, and their associated diseases
Definitions

• **Hormone** – to excite (Sir Ernest Starling 1905)

• **Endocrine** (within/separate) glands ‘pour’ secretions into blood stream (thyroid, adrenal, beta cells of pancreas)

• **Exocrine** (outside) – glands ‘pour’ secretions through a duct to site of action (pancreas - amylase, lipase)

Hormone action

• **Endocrine** – blood-borne, acting at distant sites

• **Paracrine** – acting on adjacent cells

• **Autocrine** – feedback on same cell that secreted hormone
## Hormones

<table>
<thead>
<tr>
<th></th>
<th>Water-soluble</th>
<th>Fat-soluble</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transport</td>
<td>Unbound</td>
<td>Protein bound</td>
</tr>
<tr>
<td>Cell interaction</td>
<td>Bind to surface receptor</td>
<td>Diffuse into cell</td>
</tr>
<tr>
<td>Half-life</td>
<td>short</td>
<td>long</td>
</tr>
<tr>
<td>Clearance</td>
<td>fast</td>
<td>slow</td>
</tr>
<tr>
<td>Examples</td>
<td>Peptides, monoamines</td>
<td>Thyroid hormone, steroids</td>
</tr>
</tbody>
</table>

Peptides/monoamines – stored in vesicles
Steroids – synthesised on demand
Hormone Classes

1. Peptides

- Vary in length – TRH: 3 amino acids, Gonadotrophins: 180 amino acids
- Linear or ring structures
- Two chains and may bind to carbohydrates e.g. LH, FSH
- Stored in secretory granules, hydrophilic, water soluble
- Released in pulses or bursts
- Cleared by tissue or circulating enzymes
Peptide Hormones – Granular Store

Synthesis: Preprohormone → Prohormone

Packaging: Prohormone → Hormone

Storage: Hormone

Secretion: Hormone
Surface receptor and secondary messenger activation

Insulin receptor

1. Binding of insulin to receptor proteins
2. Phosphorylation of receptor
   - Tyrosine kinase now active
3. Phosphorylation of signal molecules
   - Cascade of effects
   - Glucose uptake and anabolic reactions
Hormone Classes

2. Amines

Other amines – derivatives of tryptophan
- 5Hydroxytryptamine
- melatonin

Cortisol potentiation

COMT

Normetanephrines

MAO

VMA

Metanephrines

MAO
Adrenoceptor Activation and Secondary Messengers

Stimulate the sympathetic nervous system – fight-or-flight response

alpha-adrenoceptor

beta-adrenoceptor
Hormone Classes

3. Iodothyronines

- Thyroid hormones are not water soluble; 99% is protein bound
- Only 20% of T3 in the circulation is secreted directly by thyroid
- Secretory cells release thyroglobulin into colloid – acts as base for thyroid hormone synthesis
- Incorporation of iodine on tyrosine molecules to form iodothyrosines
- Conjugation of iodothyrosines gives rise to T3 and T4 and stored in colloid bound to thyroglobulin
- TSH stimulates the movement of colloid into secretory cell, T4 and T3 cleaved from thyroglobulin
Synthesis Thyroxine (T4) and T3

1. Thyroglobulin is synthesized and discharged into the follicle lumen.
2. Iodide (I^-) is trapped (actively transported in).
3. Iodide is oxidized to iodine.
4. Iodine is attached to tyrosine in colloid, forming DIT and MIT.
5. Iodinated tyrosines are linked together to form T3 and T4.
6. Thyroglobulin colloid is endocytosed and combined with a lysosome.
7. Lysosomal enzymes cleave T4 and T3 from thyroglobulin and hormones diffuse into bloodstream.

Capillary

Rough ER

Golgi apparatus

Thyroid follicular cells

Colloid

Tyrosines (part of thyroglobulin molecule)

Iodine

DIT

MIT

Thyroglobulin colloid

Lysosome

T4

T3

T4

T3

To peripheral tissues

Colloid in lumen of follicle

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1. Cell Membrane (peptide)

2. Cytoplasm (steroid)

3. Nucleus (thyroid)

**Hormone Receptor Location**

**Steroid Receptor Family**
- Glucocorticoids - cortisol
- Mineralocorticoids - aldosterone
- Androgens - testosterone
- Progesterone

**Nuclear receptor Family**
- Oestrogen
- Thyroid Hormone
- Vitamin D
Hormone Classes

4. Cholesterol derivatives and steroids

i) Vitamin D

- Fat soluble
- Enters cells directly to nucleus to stimulate mRNA production
- Transported by Vitamin D binding protein
Hormone Classes

4. Cholesterol derivatives and steroids

ii) Adrenocortical and gonadal steroids
- 95% protein bound
After entering cell
- Pass to nucleus to induce response
- Altered to active metabolite
- Bind to a cytoplasmic receptor

Not too rapid inactivation
- In liver by reduction and oxidation, or conjugation to glucuronide and sulphate groups
Steroids
Steroid action

Intracellular steroid pathway

Steroid hormone diffuses through plasma membrane and binds to receptor

Receptor-hormone complex enters nucleus

Receptor-hormone complex binds to GRE

Binding initiates transcription of gene to mRNA

mRNA directs protein synthesis
Control of Hormone Secretion

- Basal secretion – continuously or pulsatile
- Superadded rhythms e.g. day-night cycle – ACTH, prolactin, GH and TSH
- Release inhibiting factors – dopamine inhibiting prolactin, sum of positive and negative effects (GHRH and somatostatin on GH)
- Releasing factors
Diurnal Rhythms

- Cortisol
- Testosterone (?)
- Prolactin
- LH (?)
- Growth hormone
- FSH (?)
Control of Hormone Action

• **Hormone metabolism** – increased metabolism to reduce function

• **Hormone receptor induction** – induction of LH receptors by FSH in follicle

• **Hormone receptor down regulation** – hormone secreted in large quantities cause down regulation of its target receptors

• **Synergism** – combined effects of two hormones amplified (glucagon with epinephrine)

• **Antagonism** - one hormone opposes other hormone (glucagon antagonizes insulin)
Feedback Control

Negative Feedback

Positive Feedback
Different Negative Feedback Loops

- Long loop negative feedback
- Short loop negative feedback
- Ultra short loop negative feedback
MRI of normal pituitary gland

- Anterior pituitary
- Posterior Pituitary
- Pituitary stalk
- Optic chiasm
- Hypothalamus
Pituitary and surrounding anatomy

- Pituitary gland
- Optic chiasm
- Intracranial carotid artery
- Cavernous sinus
- Temporal lobe
- Intracavernous carotid artery
- Oculomotor nerve (III)
- Trochlear nerve (IV)
- Abducent nerve (VI)
- Ophthalmic nerve (V₁)
- Maxillary nerve (V₂)
- Sphenoid sinus
Hypothalamic neurons synthesize oxytocin or ADH.

Oxytocin and ADH are transported down the axons of the hypothalamic-hypophyseal tract to the posterior pituitary.

Oxytocin and ADH are stored in axon terminals in posterior pituitary.

When hypothalamic neurons activated, hormones released.
Control of vasopressin release and its actions

![Diagram showing the control of vasopressin release and its actions](image-url)
Oxytocin action

- PVN to Hypothalamus
- SO to Hypothalamus
- MB

- Anterior lobe
- Neural lobe

- Oxytocin

- Myoepithelial cells (mammary glands)
  - Suckling

- Uterus, cervical dilatation
  - Estrogens
  - Uterine contractions

- Milk ejection
- Labor
Anterior Pituitary

GHRH, GHIH, CRH, TRH, GnRH, Dopamine

Thyrotrophs  Corticotrophs  Gonadotrophs  Somatotrophs  Lactotrophs
Pituitary Dysfunction

- Tumour mass effects
- Hormone excess
- Hormone Deficiency

Investigations
- Hormonal tests
- If hormonal tests abnormal or tumour mass effects perform MRI pituitary
The pituitary as the ‘conductor of the orchestra’
Growth Hormone

Feedback

- Inhibits GHRH release
- Stimulates GHIH release
- Inhibits GH synthesis and release

Hypothalamus secretes growth hormone–releasing hormone (GHRH), and GHIH (somatostatin)

Anterior pituitary

Growth hormone (GH)

Indirect actions
(growth-promoting)

Liver and other tissues

- Produce Insulin-like growth factors (IGFs)

Direct actions
(metabolic, anti-insulin)

- Effects

Skeletal
- Increased cartilage formation and skeletal growth

Extraskeletal
- Increased protein synthesis, and cell growth and proliferation

Fat metabolism
- Increased fat breakdown and release

Carbohydrate metabolism
- Increased blood glucose and other anti-insulin effects

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Hypothalamo-pituitary-thyroid axis

Hypothalamus → TRH → Anterior pituitary → TSH → Thyroid gland

Thyroid hormones
Thyroid gland and Thyroid Hormones

(a) Gross anatomy of the thyroid gland, anterior view

(b) Photomicrograph of thyroid gland follicles (145x)
Thyroid Hormone Function

- Accelerates food metabolism
- Increases protein synthesis
- Stimulation of carbohydrate metabolism
- Enhances fat metabolism
- Increase in ventilation rate
- Increase in cardiac output and heart rate
- Brain development during foetal life and postnatal development
- Growth rate accelerated

In periphery T4 converted to T3
Half life T4 – 5 to 7 days
Half life T3 – 1 day
Hypothalamo-pituitary-adrenal axis & Cortisol Actions

- Major metabolic and stress hormone
The Adrenal Gland

(a) Drawing of the histology of the adrenal cortex and a portion of the adrenal medulla

- Capsule
- Zona glomerulosa
- Zona fasciculata
- Zona reticularis
- Adrenal medulla
Adrenals

Steroids

- Mineralocorticoids
  - aldosterone
- Glucocorticoids
  - cortisol
- Androgens
  - androstenedione
  - dihydroepiandrosterone (DHEA)

Epinephrine
Norepinephrine
# Renin-Angiotensin System

<table>
<thead>
<tr>
<th>Primary regulators</th>
<th>Other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Blood volume and/or blood pressure</td>
<td>↑ Blood pressure and/or blood volume</td>
</tr>
<tr>
<td>↑ K⁺ in blood</td>
<td>Stress</td>
</tr>
<tr>
<td>Kidney</td>
<td>Hypothalamus</td>
</tr>
<tr>
<td>Renin</td>
<td>CRH</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Anterior pituitary</td>
</tr>
<tr>
<td>Direct stimulating effect</td>
<td>ACTH</td>
</tr>
<tr>
<td>Initiates cascade that produces</td>
<td>Atrial natriuretic peptide (ANP)</td>
</tr>
</tbody>
</table>

**Sympathetic & Low Na**

- Zona glomerulosa of adrenal cortex
- Enhanced secretion of aldosterone
- Targets kidney tubules
- ↑ Absorption of Na⁺ and water; increased K⁺ excretion
- ↑ Blood volume and/or blood pressure

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Adrenal Hormones in Stress

Short-term stress

- Nerve impulses
- Spinal cord
- Preganglionic sympathetic fibers
- Adrenal medulla (secretes amino acid-based hormones)
- Catecholamines (epinephrine and norepinephrine)

Short-term stress response
- Heart rate increases
- Blood pressure increases
- Bronchioles dilate
- Liver converts glycogen to glucose and releases glucose to blood
- Blood flow changes, reducing digestive system activity and urine output
- Metabolic rate increases

Prolonged stress

- Hypothalamus
- CRH (corticotropin-releasing hormone)
- Corticotropic cells of anterior pituitary
- ACTH
- Adrenal cortex (secretes steroid hormones)
- Mineralocorticoids
- Glucocorticoids
- To target in blood

Long-term stress response
- Kidneys retain sodium and water
- Blood volume and blood pressure rise
- Proteins and fats converted to glucose or broken down for energy
- Blood glucose increases
- Immune system suppressed
Gonads - Steroidogenesis

**Ovarian Follicle**

- **FSH**
  - Granulosa cell
    - estrogen
    - androgen
    - aromatase
  - Theca cell
    - androgen
    - cholesterol
- **LH**

**Testis**

- Hypothalamus
  - GnRH
- Anterior pituitary
- FSH
- LH
- Leydig cells
  - Testosterone (T)
  - Spermatogonium
  - Spermatocyte
- Sertoli cell
- Testes
  - Cell products
  - Androgen-binding protein (ABP)
  - To body for secondary effects
  - Inhibin
  - Sertoli cell
  - Second messenger
Hyperprolactinaemia – Prolactin Secretion

PIF: Dopamine

PRF
- TRH
- VIP
- Oxytocin

PROLACTIN SECRETION

higher centres

hypothalamus

dopamine

optic chiasm

portal vessels

hypophyseal artery

anterior pituitary

prolactin secretion suppressed
Endocrine Tissues

Pituitary
Thyroid
Parathyroid
Adrenal
Pancreas
Ovary
Testes

Other hormones

- Heart
  atrial natriuretic peptide
- Liver
  insulin-like growth factor I (IGF-I)
- Kidney
  erythropoietin
- G/I Tract
  gastrin, incretin
- Lung
  hormone metabolism
- Blood Vessels
  prostanoids, nitric oxide, endothelin
Further Reading

The Endocrine System: An Overview
http://classes.midlandstech.edu/carterp/Courses/bio211/chap16/chap16.htm

Lecture Notes on Endocrinology – William Jeffcoate

Vander’s Human Physiology – Eric Widmaier, Hershel Raff, Kevin Strang
lipocortin -ve

Begin

Membrane phospholipid

Phospholipase A₂

Arachidonic acid

Cyclooxygenase

Cyclic endoperoxides

Prostaglandins

Thromboxanes

Lipoxygenase

Leukotrienes