

# **Introduction to Endocrine System.**

## **I. Introduction.**

Hormones may be defined as chemical substances that are secreted by living cells, and upon delivery by the circulation to a specific site, act to regulate reactions that elicit a typical response. This kind of action is endocrine.

Paracrine – acting on adjacent cells (e.g. somatostatin)

Neurocrine – secreted at nerve endings.

Autocrine – acting on the cell that secretes it.

Endocrine system.

Endocrine gland

Blood

Target organ (receptors)

## Endocrine system.

1. Structure/synthesis.
2. Physiological effects.
3. Regulation of synthesis & secretion.
4. Disorders.

Causes, etiology

Signs & symptoms

Diagnoses

Treatment

## II. Chemical structures of hormones.

Proteins (e.g. prolactin) or peptides (e.g. glucagon)

Steroids (e.g. cortisol)

Amines, derivatives of amino acids (e.g. adrenaline)

Prostaglandins & cytokines (local hormones)

Steroid hormones are not stored.

### III. Plasma levels and metabolic clearance.

Blood level depends on rate of secretion and rate of removal from blood.

Metabolic clearance = volume of plasma completely cleared of a hormone per unit time.

Relations with:

- a. binding to plasma proteins (thyroid hormones, steroids)
- b. half-lives.
- c. duration for hormone action  
minute-to-minute regulation vs long-term

## IV. Rhythms of secretion.

Episodic secretion – many hormones are not secreted continuously, but in pulses e.g. LHRH.

Diurnal rhythm – e.g. cortisol secretion is highest in the morning and lowest in the evening.

Cyclic secretion – some are secreted in complicated cycles coinciding with reproductive events e.g. LH, FSH and oestrogens.

## V. Negative and positive feedbacks.

### Characteristics

Negative feedback – to keep the level more or less constant (important for homeostasis)

positive feedback – to make the level deviate more and more from the norm (important for amplification of level for action).

↓ Oestrogen → ↑ LH → ↑ oestrogens → ↓ LH  
→ ↓ oestrogens

↓ oestrogens → ↑ LH → ↑ oestrogens → ↑ LH  
→ ↑ oestrogens

## VI. Hormone receptor relationship.

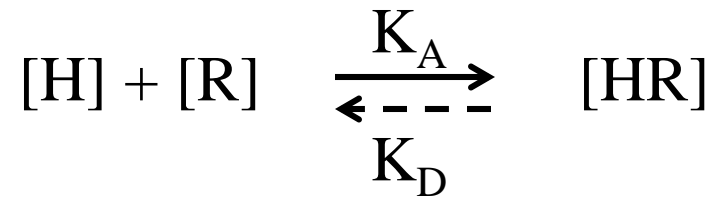
The relationship between bound and free hormones.

The Scatchard plot

Dissociation ( $K_d$ ) and association ( $K_a$ ) constants

Maximum binding ( $B_{max}$ )

Scatchard plot.



(where H is the free hormone, R, the free receptor and HR is the bound hormone)

$$\frac{[HR]}{[H][R]} = K_A$$

$$\frac{[HR]}{[H]} = K_A \times [R]$$

$$= K_A \times (R_0 - [HR])$$

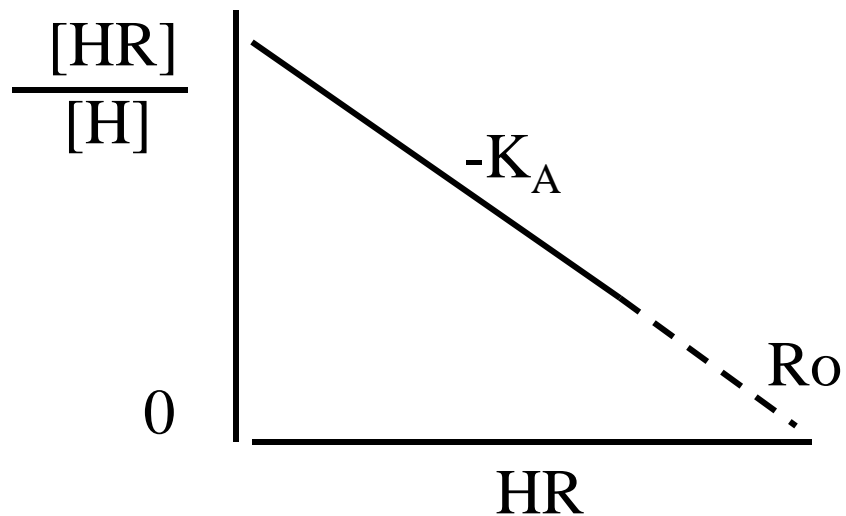
where  $R_0$  = total no. of receptors

$$\frac{[\text{HR}]}{[\text{H}]} = -K_A \times [\text{HR}] + K_A \times R_0$$

When  $[\text{H}] \longrightarrow$  infinity

$$\frac{[\text{HR}]}{[\text{H}]} = 0 \quad K_A \times [\text{HR}] = K_A \times R_0$$

$$[\text{HR}] = R_0$$



## VII. Mechanisms of hormone actions.

Mobile receptor model – steroid hormones  
(receptors in the nucleus)

fixed receptor model – peptides, catecholamines  
(receptors on the plasma membrane)

mechanisms involved – 1. cAMP.

2. calcium.

3. diacylglyceride & inositol  
triphosphate.

“multiple receptors” – thyroid hormones, receptors in  
the nucleus, plasma membrane, and/or  
mitochondria.

# Physiological actions of hormones.

## I. Introduction.

Both level of a hormone and its receptors are important.

Receptor – up or down regulation → affect response.

receptor defect → lack of action (e.g. nephrogenic  
diabetes insipidus)

peripheral resistance (thyroid  
hormones)

Conversion to active form: e.g.  $T_4$  to  $T_3$

testosterone to DHT

## II. Some ways through which hormones act.

### a. Control of membrane permeability.

This regulates the availability of substrates ions, co-factors etc.

e.g.  $T_4$  & insulin affect glucose and amino acid transport &

Na & K flux

aldosterone & vitamin D affect epithelial transport.

### b. Nuclear regulation.

Certain actions of steroid, thyroid and peptide hormones are brought about by increasing a few specific mRNAs.

c. Control of protein synthesis.

This can be exerted at the level of RNA synthesis (steroids) or at the level of the ribosomes (GH & insulin). cAMP can also induce protein synthesis either at the level of transcription (glucagon) or ribosome (ACTH).

d. Enzyme activation.

Many effects of peptide hormones and catecholamines on intracellular enzymes involve alterations in the activity of pre-existing enzymes by phosphorylation and dephosphorylation e.g insulin on glycolytic enzymes.

cAMP – phosphorylation → activate lipase &  
phosphorylase

insulin- dephosphorylation

→ activate phosphofructokinase  
inactivate fructose - 2,6 - bisphosphatase

e. Permissive action.

In some cases a hormone has to be present for some other hormones to work, yet the hormone itself does not stimulate the process. e.g. cortisol, thyroid hormones.

By inhibiting phosphodiesterase and hence the destruction of cAMP, cannot generate cAMP.

### III. 3 ways to change the rate of a biochemical reaction.

1. change the enzyme activity.  
e.g. insulin on glycolytic enzymes
2. increase the substrate.  
e.g. insulin on glycolysis by  
increasing glucose.
3. increase the end-product.  
e.g. FFA on glycolysis (through ↑ in  
acetyl CoA).

(end-product inhibition)

#### IV. Principles of hormonal integration.

(1) Redundancy (safe-guard; fine tuning).

e.g. adrenaline and glucagon on liver glycogen

(2) Reinforcement (different ways, same end).

e.g. cortisol – mobilizes amino acids from proteins  
increases enzymes for gluconeogenesis

(3) Push-pull (opposite effects on antagonistic mechanisms).

e.g. GRH & SRIF on GH secretion.  
glucose or sympathetic n.s. on insulin  
and glucagon secretion.

(4) Modulation of responding system.

Receptors –down-regulation

e.g. T4 on TRH receptors (thyrotrophs)

- up-regulation

e.g. oestrogens on LH receptors in  
granulosa cells

numbers, affinities

post-receptor (permissive) e.g. through  
inhibiting cAMP destruction.

Actions controlled by enzyme, not receptors.

11- $\beta$  hydroxysteroid dehydrogenase

- (1) Cortisol can bind to mineralocorticoid (aldosterone) receptor, but its binding site at position 11 needs a hydroxyl group, which is destroyed by the above enzyme.
- (2) Aldosterone escapes by conversion into the hemiacetal form.

## Biphasic actions of thyroid hormone.

Glycogen  
Triglyceride  
Protein

Increase  $\rightarrow$   $\uparrow$  formation

Increase too much  $\rightarrow$   $\uparrow$  breakdown

Result = difference between the 2

Futile cycle

A hormone with its direct action opposite to its permissive action (cortisol).

In time of plenty      Direct: ↑ gluconeogenesis

↑ glycogen formation

In between meals      Permissive : ↑ glycogenolytic actions  
of glucagon & adrenaline

Examples of too much or too little of the same hormones leading to the same clinical features.

(1) cortisol on muscle contraction (muscle weakness).

Too much: loss of muscle protein

Too little: ↓ neuromuscular transmission

(2) aldosterone on increase in urinary output.

Too little: ↓ sodium/water reabsorption

Too much: kidney damage, thirst

# **Regulation of endocrine secretion.**

## **I. Introduction.**

Modes of regulation.

1. humoral – hormones (releasing factors, trophic hormones).  
metabolites (glucose), ions
2. neural – neuroendocrine, autonomic nervous system.
3. negative feedback.

## II. General principles.

1. positive & negative feedbacks.

(up-regulation & down-regulation of receptors)

2. push & pull mechanisms.

under dual control by agents that either  
stimulate or inhibit

e.g. control of GH by GRH and SRIF.

### III. External and internal factors.

External factors – the open loop

e.g. lighting, stress, cold

Internal factors – the close loop (negative feedback)

e.g. metabolites – glucose

blood pressure or volume.

## IV. Hypothalamico-pituitary axis.

### 1. Regulation of anterior pituitary hormones.

controlled by releasing and inhibiting hormones, released at the median eminence and carried by the portal blood vessels to the pituitary.

### 2. Regulation of posterior pituitary hormones.

by action potential traveling down the axon to the posterior pituitary.

# Negative feedback

- (1) Long loop – Glucose and somatomedin (IGF) on GH.
- (2) Short loop – GH on somatostatin (SRIF, GH inhibiting hormone).
- (3) Ultra-short loop – GHRH on SRIF; GH on pituitary response to GHRH.

## Target gland hormone vs pituitary hormone

Primary disorders: ↓ target gland hormone  
↑ pituitary hormone

Secondary disorders: ↓ pituitary hormone  
↓ target gland hormone

## Examples of integration of control.

- (1) Effects of ANP of sodium/water excretion.
- (2) Regulation of blood glucose level.
- (3) Control of plasma calcium level.

Parathyroid hormone (PTH) - ↑ bone resorption  
↑ renal  $\text{Ca}^{++}$  &  $\text{PO}_4^{---}$  reabsorption  
↑  $\text{PO}_4^{---}$  excretion  
↑ GI absorption of  $\text{Ca}^{++}$  &  $\text{PO}_4^{---}$   
(via in ↑  $1,25 (\text{OH})_2 \text{D}_3$ )

calcitonin - ↓ bone resorption  
↓ renal  $\text{Ca}^{++}$  reabsorption  
↓ GI absorption of  $\text{Ca}^{++}$  &  $\text{PO}_4^{---}$   
(via a ↓ in  $1,25 (\text{OH})_2 \text{D}_3$ )

vitamin D - ↑ bone resorption  
↑ GI absorption of  $\text{Ca}^{++}$  &  $\text{PO}_4^{---}$

## Regulation.

PTH – secretion increased by low blood  $\text{Ca}^{++}$ .

Calcitonin – secretion increased by high blood  $\text{Ca}^{++}$ ; also by GI hormones esp. gastrin.

Vitamin D – formation of the active form increased by high PTH, low  $\text{Ca}^{++}$  & low  $\text{PO}_4^{---}$

insulin - ↑ glucose uptake (muscles, liver)  
↑ glycogenesis  
↓ gluconeogenesis  
↓ protein breakdown  
↓ lipolysis

glucagon/adrenaline - ↑ glycogenolysis  
↑ lipolysis

GH/cortisol - ↑ gluconeogenesis  
(glycerol, amino acids)  
↓ glucose uptake  
↑ glycogenolysis (cortisol, permissive)  
↑ lipolysis

thyroid hormones - ↑ glycolysis  
↑ glycogen formation/breakdown  
↑ gluconeogenesis  
↑ lipogenesis/lipolysis  
↑ protein formation/breakdown

FFA-glucose cycle:

↑ lipolysis → ↑ FFA → ↓ glucose utilization & uptake.

## Regulation:

- (1) Insulin & glucagon secretion are regulated by blood glucose, blood amino acids, GI hormones & sympathetic activity.
- (2) Adrenaline secretion is regulated by sympathetic activity (stress, blood glucose).
- (3) GH secretion is regulated by GRH, blood glucose and amino acids
- (4) Cortisol secretion is regulated by ACTH, which is regulated by CRH, negative feedback by free cortisol, & stimulated by decrease in blood glucose & stress.
- (5) Thyroid hormone secretion is regulated by TSH, which is regulated by TRH, and negative feedback by free  $T_4$ .

## Introduction to endocrine disorders.

### A. Different levels.

(1) synthesis/secretion  
hypo/hyper-secretion  
primary vs secondary

(2) conversion/delivery

(3) Receptors

### B. Hypo vs Hypersecretion.

Autoimmune

Enzyme defect

Tumours (including ectopic)

Iatrogenic

## II. Cushing's syndrome.

1. Causes – due to excess cortisol secretion.

3 types: Cushing's disease (pituitary), ectopic ACTH syndrome, and adrenocortical tumour.

2. Clinical features.

trunk obesity

moon face

plethora (redness in the face)

excessive bruising

muscle weakness

hypertension

hyerglycaemia

skin pigmentation (ACTH)

### 3. Diagnoses.

- a. dexamethasone suppression test.
- b. ACTH measurement.

### 4. Treatments.

- a. surgery (adrenal or pituitary).
- b. drugs (to block steroidogenesis).

## II. Hyperthyroidism.

1. Cause- due to thyroid –stimulating immunoglobulins (TSI) (Grave's disease)

2. Clinical features.

enlarged thyroid

tachycardia

↑ cardiac output

↑ sweating (↑ metabolism)

nervousness

weight loss (though appetite ↑)

(due to ↑ lipolysis, ↑ proteolysis)

extra-thyroidal – Exophthalmos

3. Diagnoses.

- a. serum free  $T_3/T_4$ .
- b. TRH stimulation test.
- c. Thyroid anti-body test.

4. Treatment.

- a. anti-thyroid drugs.
- b. partial thyroidectomy.
- c. radioactive iodine.