

CONCEPTS IN ENDOCRINOLOGY

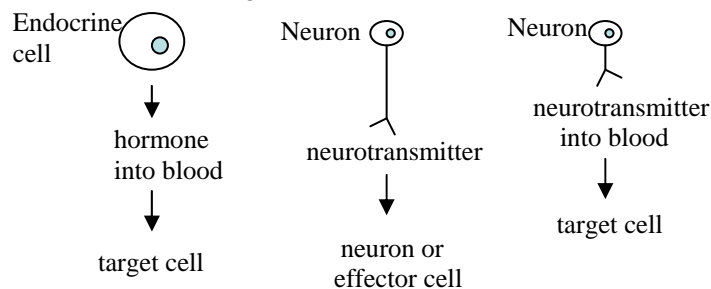
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LEARNING OBJECTIVES

- Define hormone, target cell, and receptor.
- Contrast the terms endocrine, paracrine, autocrine, and neuroendocrine based on the site of release and the pathway to the target tissue.
- Contrast peptide, steroid and amine hormones in terms of receptor location and signal transduction, solubility in blood and transport in blood.
- Explain the effects of hormone binding proteins (carriers) on access of hormones to their sites of action, degradation, and the regulation of hormone secretion.
- Explain the effects of secretion, excretion, degradation, and volume of distribution on the concentration of a hormone in blood plasma.
- Explain how endocrine cells act as signal integrators.
- Explain how negative feedback, feed-forward, and positive feedback systems work.
- Describe the principles and limitations of RIA and bioassays (stimulation/suppression tests).
- Explain the classification of endocrine pathologies.

HOMEOSTATIC CONTROL

Homeostatic control mechanisms include reflex loops in which the response decision is made at a distance from the target cell.



There are two general classes: endocrine and neuroendocrine.

Endocrine: hormone reaches its site of action via the blood circulation.

Neuroendocrine: hormone is secreted from neurons into the blood to act at a distance.

The other homeostatic control mechanism is the local response in which the signal and action occurs close to or at the target cell.



Paracrine: cytokine is secreted into the interstitial fluid to act locally on target cells.

Autocrine: cytokine is secreted into interstitial fluid to act on the cell that produced it.

FUNCTIONS OF HORMONES

Endocrine system coordinates and integrates cellular activity within the whole body by chemicals (hormones) delivered by blood.

Specific missions are to:

- Regulate sodium and water balance
- Regulate calcium balance
- Regulate energy balance
- Coordinate processes that cope with stressful environments
- Coordinate growth and development.
- Coordinate processes associated with reproduction and lactation.

EFFECT DEPENDS ON BLOOD LEVEL

Hormones are secreted into the blood stream and circulate throughout the body at very low concentrations (pMolar to nMolar). Therefore, their rate of production, delivery, and turnover are important control sites.

- Rate of production
 - A. most regulated aspect
 - B. mediated by (+) and (-) feedbacks
- Rate of delivery
 - A. dependent on perfusion and blood flow
 - B. follows mass action laws (carriers)
- Rate of degradation and /or excretion

CLASSIFICATION BY STRUCTURE & SOLUBILITY IN PLASMA

There are three general types of hormone molecules: peptides, steroids, and amines. They differ in their relative solubility in plasma.

Peptide hormones consist of three or more amino acids and are soluble in blood.

Steroid hormones are derived from cholesterol and are insoluble in blood.

Amine hormones are derivatives of amino acids and some are soluble in blood.

Peptides and proteins: are synthesized, packaged, and transported as other secretory proteins. Most are synthesized initially as **preprohormones** which in the rough endoplasmic reticulum (RER) are cleaved to remove the signal sequence forming the **prohormone** (Fig 1). Later in the Golgi, the prohormones are packaged, trimmed into an active hormone, and stored in vesicles. Peptide hormones are usually secreted in bursts in response to stimuli.



Figure 1. Peptide hormone processing.

Steroid hormones: are derived from cholesterol. They are made only in the adrenal cortex, gonads and in pregnant women in the placenta. The first and rate limiting step in the synthesis of all steroid hormones is conversion of cholesterol to **pregnenolone**. Pregnenolone is formed on the inner membrane of the mitochondrion, and then shuttled between the mitochondrion and the smooth endoplasmic reticulum for further enzymatic transformations. Steroid hormones are synthesized on demand. They are not stored. Steroid hormones can be converted to more active (or less) active hormones within their target tissues.

Amine hormones: are derivatives of amino acids.

- **Thyroid hormones** (T_3 and T_4) contain “double tyrosines” covalently bound to iodine atoms. T_4 can be converted to T_3 within target tissues.
- **Catecholamines:** Epinephrine (Epi) is a hormone; norepinephrine (NorEpi) functions as a hormone and as a neurotransmitter.

DELIVERY BY TRANSPORT CARRIERS

Peptide hormones are soluble in blood. They are degraded by the liver and then cleared by the kidney with half-lives of a few minutes.

Steroid hormones and **thyroid** hormone are not soluble in blood. They circulate bound to protein carriers. Binding to the transport carrier protein extends the half-life of the hormone in the blood (60-90 minutes for steroids, several days for thyroid hormone).

The carrier-hormone complexes sequester the hormone from its target cell with most of the hormone in the bound state. The concentration of free plus bound equals total hormone concentration in the blood **but only free is active**.

RECEPTORS DETERMINE SPECIFICITY

Hormones are widely distributed throughout the body and have access to all cells but only target cells respond because they possess a receptor for the hormone. The receptor contains a recognition site that binds its hormone with high affinity and selectivity. A cell may express thousands to tens of thousands of receptors for a single hormone.

The lipid solubility of the hormone dictates the cellular location of its receptor. Plasma insoluble hormones bind to intracellular receptors; plasma soluble hormones bind to cell surface receptors.

Thyroid and steroid hormones bind to intracellular receptors to activate transcription. This results in synthesis of new proteins and therefore is a slow response (30 minutes or more).

Peptide hormones bind to cell surface receptors which activate a second messenger (Fig 2). This results in a rapid (seconds) change in function/metabolism. Second messengers are important because they provide:

- **Amplification:** One hormone molecule can generate thousand of copies of second messenger (e.g., cAMP) and thereby affect many copies of responsive target molecules (effectors) in the cell.

- **Memory:** Once activated the second messenger stays on for several seconds to minutes.
- **Complex regulation:** Multiple pathways can be initiated by binding one hormone to a single receptor type (Fig 2).

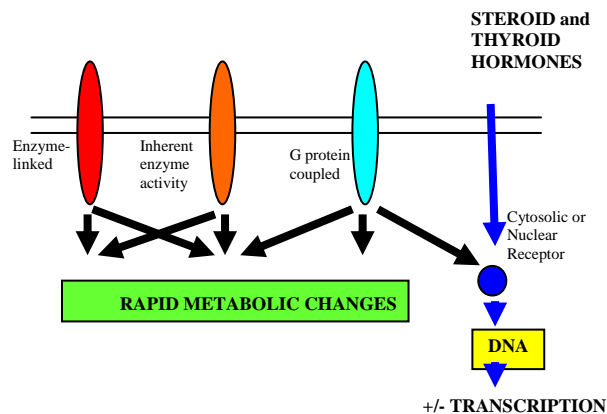


Figure 2. Typical signal transduction pathways for hormone receptors.

The duration of a response depends on how long the hormone is available (i.e., its half life) and the time period of its biological response.

Adaptation or desensitization of receptors: diminishes the cell's response when the level of hormone is chronically elevated.

Rebound: is increased sensitivity of the target cell to a hormone due to its prolonged absence. In this instance the target cell increases its receptor numbers in an attempt to “find” the hormone and so is “hyperactive” with return of the hormone.

REGULATION OF HORMONE SECRETION

Hormone secretion is governed by one of three types of regulatory stimuli: neural, hormonal, and nutrient (or ion). These stimuli activate a reflex loop in which the endocrine cell(s) is the effector. These reflex loops are typically **negative feedback loops.**

Hormones seldom work alone. Other interactions include:

Feed forward primes a target tissue. For example, the smell of food alone causes gastrin to be secreted by the stomach (antrum) which stimulates HCl secretion from the corpus/fundic stomach.

Synergy occurs when the net effect of several hormones acting on a target tissue causes a bigger response than simple addition of each independent hormonal effect.

Re-enforcement occurs when the actions of a single hormone on multiple tissues converge to regulate a process such as glucose production (see Fig 3).

Permissiveness (or tropism) occurs when the actions of a tropic hormone sensitize the target tissue to a second hormone. For example, maturation of the male gonads is dependent on the presence of the sex hormone, testosterone. However, the fetus will not grow unless thyroid hormone is present. Thyroid hormone (a tropic hormone) itself can not trigger maturation of the gonads but leads to the expression of testosterone receptors that govern this differentiation process.

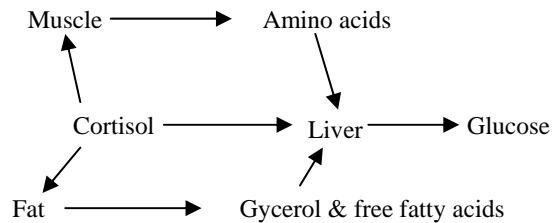


Figure 3. Cortisol acts on muscle and fat to *re-enforce* the production of glucose from the liver.

INACTIVATION OF HORMONE SIGNALLING

Inactivation of the hormone signaling occurs at two levels. Cellular inactivation involves the termination of the receptor's response. Systemic inactivation involves homeostatic control mechanisms such as negative feedback (most common) which removes the initial stimulus (see Fig 4).

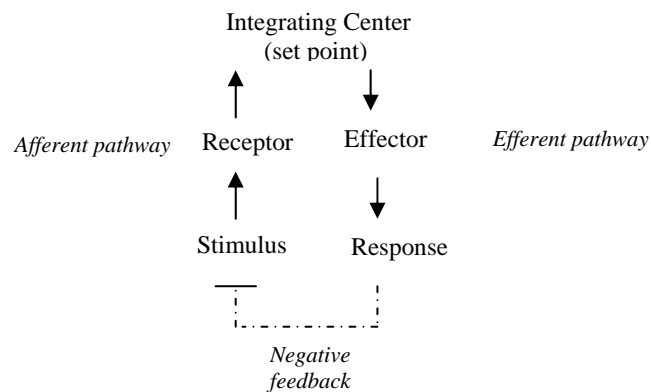


Figure 4. Negative feedback loops eliminate the initiating stimulus.

For example, the pituitary and adrenal glands are in a negative feed-back loop (Fig 5). The stimulus, hypoglycemia (low blood glucose level) leads to the secretion of cortisol from the adrenal gland. Cortisol acts on liver, muscle, and fat to raise blood glucose levels. Over ride of the set points for this loop occurs at the hypothalamus (brain) in response to inputs such as circadian rhythm and stress. Why is this important?

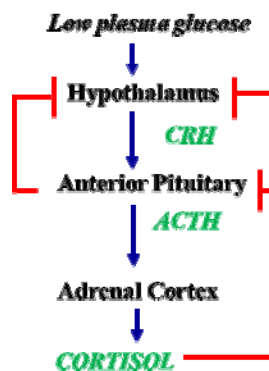


Figure 5. Negative feedback loops such as the hypothalamus-pituitary-adrenal axis have positive inputs (circadian rhythm) that transiently override the set point to govern blood glucose levels.

IMPORTANCE OF HORMONE LEVELS

Disorders of the endocrine system result from too little or too much hormone or target cell resistance.

- **Hypo-secretion:** results in an insufficiency of hormone.
- **Hyper-secretion:** results in an excess of hormone.
- **Resistance:** is an abnormal target organ response due to receptor and/or second messenger dysfunction despite adequate active hormone levels.

The hormone and its regulated substance (another hormone or another parameter) do not change independently. By monitoring both the hormone and its regulated substance, one can readily deduce the nature of the dysfunction. When the target endocrine gland itself is misbehaving, then it is referred to as a **primary pathology**. If the problem occurs in the regulating gland (pituitary), then it is a **secondary pathology**, and those due to the more distal regulator (hypothalamus) are **tertiary**. Shown in the table below are the findings indicative of pathologies associated with the cortisol axis (diagrammed in Fig 5).

Dysfunction Site:	Tertiary Pathology	Secondary Pathology	Primary Pathology
Hypothalamus	High CRH levels	Low CRH	Low CRH
Anterior pituitary	High ACTH	High ACTH	Low ACTH
Adrenal cortex	High cortisol	High cortisol	High cortisol

Because hormones are present at very low concentrations (nM) in body fluids and many have related structures, their measurement requires very high sensitivity and high specificity. Two common types of assays are used:

- **Radio-immune assay (RIA)** and **enzyme-linked immunosorbent (ELISA) assay** measure the immuno-reactivity of the hormone in the body fluid.
- **Bioassay** (suppression and stimulation) measures the biological activity to a challenge dose of hormone or substrate such as glucose (glucose tolerance test).

The results from these two assays can differ. Specifically,

- RIA measures total hormone (carrier-bound hormone plus free) but only free is active.
- RIA will detect both active and inactive hormones but the cell receptor does not.
- The hormone can be modified which alters its bio-activity but not its immuno-reactivity (and conversely).
- Certain hormones are secreted at regular intervals (pulsatile) so a randomly taken sample may have assayed either a peak or trough.

GENERAL CONCEPTS

- Peptide hormones are soluble in plasma, act via surface receptors, are fast-acting and short-lived.
- Thyroid hormones and steroid hormones are insoluble in plasma, act via intracellular receptors to change transcription, are slow-acting and are long-lived.
- Thyroid and steroid hormones can be converted to more active (or less active) hormones within target tissues.

- Transport carriers regulate hormone availability, physiologic function, and half lives.
- Hormone release can be governed by neuronal input, other hormones, nutrients and ions.
- Regulation of hormone signaling occurs most often by negative feedback to control plasma concentration of the hormone and at the target cell where hormone actions are integrated.
- Pathology in endocrinology occurs when there is either too little or too much hormone or resistance to the hormone due to receptor dysfunction.
- Interpretation of hormone levels requires consideration of either the tropic hormone(s) or of the ion/nutrient controlled by the hormone.

SUMMARY OF HORMONE CLASSES

Chemical	Response time	Effect time	Carrier	Response	function	example
peptides	fast-acting (sec-min)	short-lived	No	2° messenger cascades	homeostatic	glucagon & insulin
steroids	Slow (hours)	long-lived	Yes	transcription & translation	development homeostatic	Estrogen Cortisol
amines	fast	short-lived	No	2° messenger cascades	homeostatic	EPI
	slow	long-lived	Yes	transcription	development tropic	T4 & T3

QUESTIONS

A 25 year old male comes in to your office for evaluation. The following results were found.

Plasma cortisol at 4PM: 25 µg/dL (normal 3-15 µg/dL)

To suppress the HPA axis, you administer dexamethasone at 11PM. Sixty minutes later, the results are:

Plasma cortisol levels are 35 µg/dL (normal <5 µg/dl).

Plasma ACTH: 7pg/mL (normal, >20 mg/mL)

1. These results are consistent with an overproduction of:

- CRH from the hypothalamus
- ACTH from a pituitary
- Cortisol from the adrenal

2. You would classify this state as:

- primary endocrine pathology
- secondary endocrine pathology
- tertiary endocrine pathology

ANSWERS

- C
- A