

Endocrine Control Systems

Dave Bridges, Ph.D.

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This lecture covers the general principles of endocrine control systems. It covers the following pages in the textbook: 12; 121-124; 319-332¹. The goals of this lecture are to demonstrate the basic concepts of endocrinology including what hormones do, how they are classified and generally how they function. This is the first of seven lectures, the next six of which will go into various endocrine systems in more detail. The concepts in this lecture are essential to the understanding of the rest of the lectures. This series of lectures will focus on the normal physiology and pathophysiology of the endocrine system, but for more information about specific dental-related aspects of endocrine pathophysiology have a look at this paper².

¹ E Widmaier, H. Raff, and K. Strang. *Vander's Human Physiology: The Mechanisms of Body Function*. McGraw-Hill Science/Engineering/Math, 13th edition, 2013. ISBN 0073378305

² L. Carlos, Y. Jimenez Soriano, and Mg. Sarrion Perez. Dental management of patients with endocrine disorders. *Journal of Clinical and Experimental Dentistry*, 2(4):e196–e203, 2010. ISSN 19895488. DOI: 10.4317/jced.2.e196

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Learning Objectives

For this lecture, the learning objectives are:

- Define endocrine, paracrine, autocrine, and exocrine systems, define neurosecretory cells by giving a few examples.
- List major chemical categories of hormones and give several examples that belong to each class.
- List important factors that determine hormone levels in circulation.
- Explain cellular actions of hormones via membrane and nuclear receptors, including an understanding of the rates by which these processes can affect cells.
- Define basal secretion and stimulated secretion of endocrine glands.
- Describe negative and positive feedback system using an example.
- Explain with examples neuroendocrine integration.

General Hormonal Principles

A MAJOR ADVANTAGE OF MULTICELLULARITY, is that biological roles are divided into specialized organs and tissues. In a single cellular organism, such as *Saccharomyces cerevisiae*³, all cells need to autonomously be able to sense the environment, cellular conditions and respond appropriately. Multicellular organisms are able to use more sophisticated mechanisms to sense the environment and make these decisions. Essential to this division of labor is the ability of these organ systems to communicate efficiently and effectively with each other. This is accomplished through hormones, which are secreted from one organ to pass information along to other tissues.

³ also known as brewer's yeast

Hormonal Classification

There are hundreds, if not thousands of hormones, if defined loosely to mean *chemicals derived from one cell that can affect another cell*⁴. Remembering what these all do, how they are made, where they come from can be a challenge. To simplify this, these can be grouped several ways including chemically, anatomically, and based on relative proximity or functionally.

⁴ more specifically they are defined as: "a class of signaling molecules produced by glands in multicellular organisms that are transported by the circulatory system to target distant organs to regulate physiology and behaviour. Hormones have diverse chemical structures that include eicosanoids, steroids, amino acid derivatives, peptides, and protein.

CHEMICALLY, hormones can be small molecules such as amino acid derivatives or lipids, can be small polypeptides, or even large proteins with complex three dimensional structures (see Figure 1). The chemical type of a hormone is important for understanding how it is made, what tissues it can affect⁵, and how affects a cell⁶. Often, an endocrine organ only releases hormones of a particular chemical class. An example here is the adrenal medulla which secretes several steroid hormones, each of which have different roles and target tissues but are all the same chemical class.

ANATOMICALLY, hormones can be grouped based on where they are secreted from. Some major endocrine organs include the pancreas, the adrenal gland and the pituitary gland. Another way of considering anatomical classification of hormones is the relationship between the secreting cell and the target cell. Hormones can act on the secreting cell, or a very close cell or a cell in a (relatively) far away tissue. These are known as autocrine, paracrine and endocrine actions (see Table 1).

FUNCTIONALLY, one can group hormones together based on collective regulation of a set of organs. These are often considered *axes* and some examples include the hypothalamic-pituitary-adrenal (HPA) axis, gut-liver-brain axis or the sympathetic-adrenal-medullary (SAM) axis.

Hormonal Signaling Concepts

Hormones can be understood from a general understanding of what regulates the levels of the hormone in the body, and how and what tissues it exerts its actions. For each hormone we will examine in this unit, we will discuss the following points

- What chemical type is the hormone?
- Where is the hormone made?
- What signals cause that hormone to be released?
- What are the receptors and signaling cascades activated by this hormone?
- What tissues does this hormone affect, and how?
- How is the signal turned off

⁵ For example can it cross the blood brain barrier

⁶ For example can it cross the membrane.


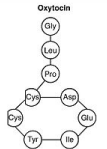

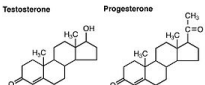
Hormone Class	Components	Example(s)
Amine Hormone	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	Norepinephrine 
Peptide Hormone	Short chains of linked amino acids	Oxytocin 
Protein Hormone	Long chains of linked amino acids	Human Growth Hormone 
Steroid Hormones	Derived from the lipid cholesterol	Testosterone Progesterone 

Figure 1: Chemical classification of hormones.

Type	Target	Example
Autocrine	Secreting cell	Monocyte IL-1
Paracrine	Nearby cell	Hedgehog
Endocrine	Far away cell	Insulin

Table 1: Types of hormones, based on the proximity of target and secreting cells

Regulation of Hormone Levels

Most signaling events are controlled at the level of hormonal secretion. For example, when the pancreas wants to communicate with the liver, it can secrete insulin or glucagon from storage vesicles. This can occur very rapidly, as long as sufficient hormone is present in the storage vesicles and the liver receptors are sufficiently prepared to respond.

SYNTHESIS AND PROCESSING OF HORMONES generally occurs from a specific cell type in a particular gland. Normally endocrine glands⁷ allow for release of stored hormones into the blood in response to a particular signal. Typically these glands synthesize the hormone, process it into an active form and store it in a state where it can be released on demand. The major glands that release hormones are the pineal, pituitary, thyroid and parathyroid glands, as well as the pancreas, ovaries, testes, hypothalamus and adrenal glands. Steroid hormones are often controlled by enzymatic activation of their synthetic pathways and released in response to specific exocytotic signals.

NEUROSECRETION IS ANOTHER MECHANISM BY WHICH HORMONES ARE RELEASED. In these cases, the hormones are synthesized and stored in the axons of specialized neurons. When these neurons receive pre-synaptic signals to fire, instead of making synaptic contacts with another neuron, they release the stored contents into the blood. Many neuroendocrine hormones released from the hypothalamus and the posterior pituitary are released this way.

SOME HORMONES ARE SECRETED UPON STIMULATION, WHEREAS OTHERS ARE RELEASED BASALLY AND WITHOUT STIMULUS. In the case of basal secretion, the hormone is released at all times, as soon as it is made and processed. Some examples of constitutive secretion are growth hormone⁸ and prolactin release. In these cases this maintains a steady level of hormone release, often to maintain long-term processes such as growth. As is the case with both GHRH and prolactin, basal secretion can also be augmented if necessary by other signals.

REGULATED SECRETION OF HORMONES occurs in response to an initiating signal. In these cases the hormone is synthesized and stored in preparation for a secretion signal. For example, in the case of insulin the pancreatic β -cells sense increases in blood glucose levels, causing a depolarization of the plasma membrane via ATP-sensitive potassium channels and allowing for exocytosis of insulin storage granules. This is described in Figure 2. This can continue as long as

⁷ as opposed to an exocrine gland, which releases its contents externally. These would include salivary, mammary and sweat glands

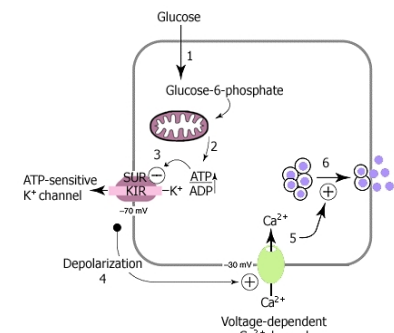


Figure 2: Mechanisms of glucose-induced insulin secretion from pancreatic β -cells.

⁸ As we will discuss in lecture 4, GH is actually a mixture of basal secretion along with secretion regulated by GHRH (Growth Hormone Releasing Hormone) and somatostatin

there is enough insulin storage granules. Most hormones have specific signaling/sensing pathways that regulate their synthesis and secretion. Some examples of these are shown in Table 2.

Principles of Hormone Receptors

ALL HORMONES HAVE RECEPTORS, either on the surface of the cell (if the hormone is not membrane soluble) or on the inside of the cell (if the hormone can cross the plasma membrane). Receptors have two key features, they must *recognize* the hormone and they must be able to *transmit* that recognition event.

HORMONES ARE RECOGNIZED by specific receptors, and can be thought of as key/lock pairs. For example the feeding hormone Leptin binds to the Leptin Receptor in the hypothalamus, causing suppression of appetite. If either of these genes are mutated then the subject is hyperphagic. Some hormones can bind to several receptors, and some receptors are capable of binding one or more hormones, increasing the potential complexity of the signaling system. When trying to understand a hormonal signaling event, it is useful to think of what the receptors are, and where they are located.

GENERALLY HORMONE RECEPTORS CAN BE GROUPED INTO CELL-SURFACE RECEPTORS AND NUCLEAR HORMONE RECEPTORS. Cell surface receptors detect the hormone signal at the cell surface then propagate that signal by activating second messengers and protein phosphorylation cascades to modify the activity of target proteins. Nuclear hormone receptors bind to the hormone *after it enters the cell*. Typically these hormones activate the receptor allowing for it to translocate to the nucleus and bind specific DNA targets (see Figure 3). These hormones typically regulate the transcription of target genes and therefore are slower acting than cell surface receptors.

The three major classes of endocrine cell-surface receptors are G-protein coupled receptors⁹, tyrosine receptor kinases and JAK/STAT receptors. GPCRs are seven transmembrane receptors that upon binding to a specific ligand, can activate a heterotrimeric G-protein. Once activated, those G-protein can have several effects depending on its type. Gs class G-proteins induce cAMP signaling by activating adenylate cyclase. Gi family proteins inhibit adenylate cyclase, thereby reducing cAMP signaling. Gq enzymes activate Ca²⁺ and diacylglycerol signaling whereas G₁₂ class proteins activate Rho GTPase signaling.

The other two main cell surface receptor classes are receptor ty-

Signal	Examples
Neural Stimulation	Adrenaline, CRH, TSH
Another Hormone	Cortisol, Thyroid Hormones
Metabolite	Insulin, Glucagon, Calcitonin
Physical Stimuli	Ghrelin, Renin

Table 2: Some examples of mechanisms by which hormone release can be stimulated.

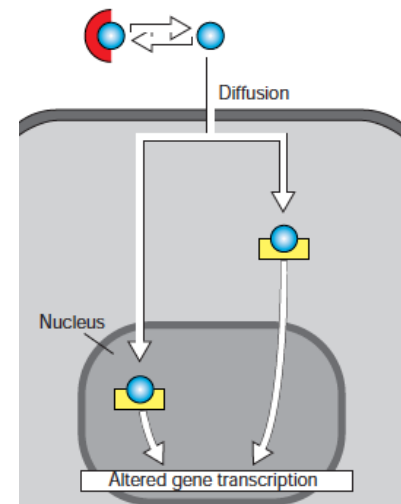


Figure 3: Mechanisms of nuclear hormone-receptor signal transduction.

⁹ GPCRs

rosine kinases and JAK¹⁰/STAT¹¹ receptors. When ligands bind to these receptors the receptor tyrosine kinases are activated and phosphorylate themselves, and other adaptor proteins. These then assemble signaling networks to cause downstream effects. Insulin and IGF-1 are examples of receptor tyrosine kinase signaling. JAK/STAT receptors recruit a kinase (called JAK) upon ligand binding, which then phosphorylates a transcription factor called STAT, which are then phosphorylated by the JAK proteins. The phosphorylated STATs translocate to the nucleus where they activate transcription. Growth hormone and Leptin exert their effects through a JAK/STAT pathway

¹⁰ Janus Kinase

¹¹ Signal Transducer and Activator of Transcription

THE TISSUE DISTRIBUTION OF HORMONE RECEPTORS is key to understanding what physiological effects the hormone may exert. As an example, insulin receptors cause dramatically different physiological effects depending on the target tissue (see Table 3).

Tissue	Effect
Pancreas	Blocks insulin secretion
Liver	Prevents gluconeogenesis, promotes glycogenesis
Fat	Glucose uptake, lipid synthesis
Hypothalamus	Reduces appetite

Table 3: Some examples of tissue-specific effects of insulin in various tissues.

Understanding what a hormone does, therefore is highly dependent on the tissue what it is acting on. Several of the hormones we will discuss in the next few lectures function through G_s-linked G-Protein Coupled Receptors which work by synthesizing cAMP and activating the protein kinase PKA. In each of these cases, PKA gets activated, but the results of PKA may activation differ from cell to cell.

HORMONES CAN REGULATE a wide variety of cellular processes. Two of these include changing metabolism rapidly via post-translational modification of key enzymes, or directing the synthesis of new transcripts, resulting in longer lasting changes in cellular physiology. For example, if a cell needs to rapidly respond to a stress signal such as adrenaline, a fast-acting second-messenger pathway¹² is activated to quickly accelerate cardiac muscle contraction. If long term changes to are required, such as the case in sex hormones, testosterone¹³ is able to activate the synthesis of new transcripts.

¹² In this case it is a G-Protein Coupled Receptor mediated activation of cAMP-dependent signaling

¹³ testosterone binds to the androgen receptor, a nuclear hormone receptor.

Negative and Positive Feedback of Hormones

Although we think quite a lot about how a hormone signaling event is initiated, just as important is the processes by which we end the

event. For example, adrenaline will accelerate our heart rate but if that went on indefinitely we would develop arrhythmia. There are two main ways in which endocrine processes can be stopped; you can reduce the amount of the circulating hormone, or you can alter the responsiveness of the target tissue. In most cases both of these processes occur. Defects in negative feedback can effectively generate the same symptoms as overproduction of the hormone.

NEGATIVE FEEDBACK OF SIGNAL TRANSDUCTION EVENTS is the primary mechanism by which a target cell can stop responding to a hormone. In the case of G-Protein coupled receptors, there is a class of compounds called arrestins that mediate this process. In this paradigm, after GPCR activation a class of kinases called GRKs (G-Protein Coupled Receptor Kinases) phosphorylate the receptor, which recruits the arrestins. The arrestin molecules now sterically prevent further G-protein activation, and further signaling from that receptor. In other cases, the cell surface receptors may be internalized or degraded or the ability of signals to be propagated from those receptors may be blocked.

REDUCTION OF SERUM HORMONE LEVELS can occur by stopping production or release of new hormones or by degrading or removing the existing hormone. In the case of cortisol signaling, its release is caused by the sequential upstream release of CRH and ACTH. Along with its effects on its intended target tissues, cortisol also acts back on the pituitary and the hypothalamus to prevent the synthesis of ACTH and CRH respectively, thereby reducing the activating signals.

Separate to this feedback mechanism, in many target tissues, cortisol also induces the synthesis of an enzyme called 11 β -hydroxysteroid dehydrogenase type 2. This enzyme converts cortisol to its less active metabolite cortisone¹⁴. This effectively reduces the cortisol levels within the target cell. In this way cortisol both reduces its synthesis (through repression of ACTH/CRH) and induces its own breakdown (through 11 β -hydroxysteroid dehydrogenase type 2).

¹⁴ H. J. Hubener, D. K. Fukushima, and T. F. Gallagher. Substrate specificity of enzymes reducing the 11- and 20-keto groups of steroids. *The Journal of biological chemistry*, 220:499–511, 1956. ISSN 00219258

MOST ENDOCRINE LOOPS HAVE BUILT-IN NEGATIVE FEEDBACK CIRCUITS. If they did not then hormonal signaling would occur in an unrestrained manner. On the other hand, too much negative feedback can also be a bad thing. In the case of insulin signaling, too much insulin action (for example as in the case of obesity) can lead to chronic insulin resistance. This in turn leads to an inability of the body to correctly dispose of glucose efficiently, eventually resulting in type II diabetes. We will discuss this in more detail in the lecture on pancreatic function and metabolic control.

ANOTHER TYPE OF FEEDBACK IS POSITIVE FEEDBACK. This is less common, and results in a hormone that amplifies its own release. An example of this is oxytocin which is released during delivery. This hormone is released by the mother's pituitary and causes contractions of the uterine lining. This stretch is sensed by the pituitary, causing more oxytocin to be released. This circuit will result in increasing amounts of both contractions and oxytocin. As with most positive feedback loops, this effect is inherently unstable and requires an external event (in this case, the delivery of the fetus) for the loop to stop self-promoting.

Neuroendocrinology

Many hormonal signaling events involve the brain, which could be considered the most complex endocrine organ. The primary role of the brain is to integrate external sensory cues¹⁵, conscious thoughts¹⁶ with internal signals¹⁷ and to determine the most appropriate response. The key parts of the brain that are involved in endocrine responses are the hypothalamus and the pituitary (Figure 4).

THE HYPOTHALAMUS¹⁸ often responds to hormones sent from either the periphery or the rest of the brain. The hypothalamus is a central node for the regulation of appetite, circadian rhythms, body temperature and behaviors. The hypothalamus can signal to other parts of the brain, including the pituitary gland making it the crossover point of the endocrine and nervous systems. We will discuss the role of the hypothalamus more in the next few lectures. Several endocrine axes exploit the proximity of these two brain regions (see Table 4):

Axis	Hypothalamic	Pituitary	Function
HPA	CRH	ACTH	Glucocorticoids
HPG	GnRH	FSH/LH	Reproductive hormones
HPT	TRH	TSH	Thyroid hormones

IT IS IMPORTANT THAT THE NERVOUS SYSTEM IS ABLE TO INTEGRATE WITH THE ENDOCRINE SYSTEM. Some endocrine responses, such as adrenaline and cortisol secretion are activated by nervous activity. Other hormones such as ghrelin and leptin, which modify appetite, start as signals in the periphery but then function on the nervous system to alter behaviors. When considering *a priori* whether a hormone has a neuroendocrine role, take into account whether this hormone is either the cause of, or is in response to a process regulated by the brain. If that is the case, then it is likely that the

¹⁵ such as sights, sounds

¹⁶ such as stress or fear

¹⁷ such as metabolite levels

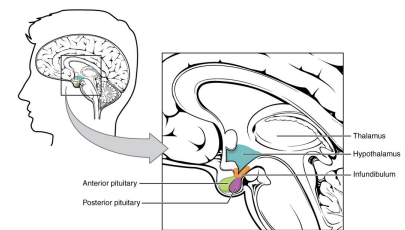


Figure 4: Location of the pituitary and hypothalamus in the human brain.

¹⁸ Under the thalamus

Table 4: Pituitary-hypothalamic axes.

hypothalamus has receptors for this hormone and plays a role in co-ordinating those effects.

IN THE NEXT LECTURE we will discuss the inter-relationships between the hypothalamus and the pituitary and how these connections regulate the hormone released from the pituitary gland.

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