Control Mechanisms 2: Endocrine Control

Hormones are chemical messengers that are secreted into the blood by endocrine cells or specialized neurons. As we will see at many times during this course, a wide variety of hormones provide for the fundamental basis of physiological control. Hormones act on their target cells in one of three basic ways:

1) Control the rate of enzymatic reactions
2) Control transport of molecules across cell membranes
3) Control gene expression and synthesis

By definition, hormones are released into the blood and have their effects at targets at some distance from their synthesis. Three general types of hormones are recognized: peptide hormones, steroid hormones, and amine hormones. Peptide hormones are comprised of three or more amino acids, steroid hormones are derived from cholesterol, and amine hormones are derivatives of single amino acids. We will largely concentrate on peptide and steroid hormones in this overview, as they are the most common and their properties are the most different. The properties of these hormones are summarized below, but in general the most fundamental difference is that steroid hormones are lipophilic whereas peptide hormones are not. Thus, steroid hormones can freely cross cell membranes whereas peptide hormones must bind to membrane-bound receptors to have effects on target cells.

<table>
<thead>
<tr>
<th>Property of Hormones</th>
<th>Peptide Hormones</th>
<th>Steroid Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis and Storage</td>
<td>Made in advance; stored in secretory vesicles</td>
<td>Synthesized on demand from precursors</td>
</tr>
<tr>
<td>Release from Synthetic Cell</td>
<td>By exocytosis</td>
<td>Simple diffusion</td>
</tr>
<tr>
<td>Transport in Blood</td>
<td>Freely dissolve in plasma</td>
<td>Bound to carrier molecules</td>
</tr>
<tr>
<td>Half-Life</td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td>Location of Receptor</td>
<td>On cell membrane</td>
<td>Usually in cytoplasm or nucleus</td>
</tr>
<tr>
<td>Response to Receptor Binding to Ligand</td>
<td>Activate second messenger systems or open ligand-gated channels</td>
<td>Activate genes for transcription and translation</td>
</tr>
<tr>
<td>General Target Response</td>
<td>Modification of existing proteins</td>
<td>Induction of new protein synthesis</td>
</tr>
<tr>
<td>Examples</td>
<td>Insulin</td>
<td>Estrogen, androgen, cortisol</td>
</tr>
</tbody>
</table>
Generally, hormones are thought to be substances that have actions on an effector (e.g., kidney, gastrointestinal tract, etc.). However, a number of hormones are tropic hormones whose actions are to control the secretion of another hormone. As will be discussed below, the hypothalamus is an important source of tropic hormones, which act on the anterior pituitary gland. In turn, the pituitary gland releases other tropic hormones that regulate hormone secretion throughout the body. In these hormonal reflex pathways, the end product provides for negative feedback earlier in the pathway. The presence of negative feedback assures that the level of the end-product hormone remains within the appropriate range.

The pituitary gland has two portions: the anterior pituitary and the posterior pituitary. The anterior pituitary (also called adenohypophysis) is a true endocrine gland of epithelial origin, whereas the posterior pituitary (also called neurohypophysis) is an extension of the neural tissue of the brain.
Hormonal release mechanisms from the anterior and posterior pituitary are completely different. Hormones released from the anterior pituitary are produced by endocrine cells located in this glandular tissue. However, the synthesis and release of these hormones is tightly controlled by the hypothalamus via tropic hormones. These tropic hormones are synthesized by hypothalamic neurons, and transported to the anterior pituitary via the *hypothalamic-hypophyseal portal system*. Recall from the first lecture that a portal system consists of two capillary beds in series with each other. Why are hypothalamic tropic hormones conveyed to the anterior pituitary via this portal system instead of through the systemic circulation? The answer is simple: by releasing the tropic hormones in this way, these agents are diluted in much less blood volume than if placed into the general circulation. Thus, the anterior pituitary endocrine cells come in contact with relatively high concentrations of the hypothalamic tropic hormones, despite the fact that these chemicals are produced in tiny quantities.

In contrast, the posterior pituitary hormones are synthesized by hypothalamic neurons that send their axons into the posterior pituitary gland. When required, these hormones are released into the vicinity of blood vessels in the posterior pituitary through a process similar to neurotransmitter release.
ANTERIOR PITUITARY HORMONES

The functions of the anterior pituitary hormones are listed below. Note that most of these hormones have as one of their functions actions on other endocrine targets. For example, Growth Hormone stimulates production of IGF-1, FSH and LH promote the secretion of sex hormones, TSH stimulates the synthesis and secretion of thyroid hormones, and ACTH promotes the synthesis and secretion of adrenal cortical hormones. Only prolactin lacks a clear tropic role on endocrine targets, although it is possible that such a role has just not been discovered. After childbirth in females, prolactin has a clear role in promoting milk secretion. However, this hormone is also present in males and in non-lactating females, where its function is not clear.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Target</th>
<th>Major Actions in Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>Thyroid gland</td>
<td>Stimulates synthesis and secretion of thyroid hormones</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)</td>
<td>Ovary</td>
<td>Stimulates growth of follicles and estrogen secretion</td>
</tr>
<tr>
<td></td>
<td>Testis</td>
<td>Acts on Sertoli cells to promote maturation of sperm</td>
</tr>
<tr>
<td>Luteinizing hormone (LH)</td>
<td>Ovary</td>
<td>Stimulates ovulation of ripe follicle and formation of corpus luteum; stimulates estrogen and progesterone synthesis by corpus luteum</td>
</tr>
<tr>
<td></td>
<td>Testis</td>
<td>Stimulates interstitial cells of Leydig to synthesize and secrete testosterone</td>
</tr>
<tr>
<td>Growth hormone (GH)</td>
<td>Most tissues</td>
<td>Promotes growth in stature and mass; stimulates production of insulin-like growth factor (IGF-I); stimulates protein synthesis</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Mammary glands</td>
<td>Promotes milk secretion and mammary growth</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone (ACTH)</td>
<td>Adrenal Cortex</td>
<td>Promotes synthesis and secretion of adrenal cortical hormones</td>
</tr>
<tr>
<td>β–lipotropin, β–endorphin</td>
<td>?</td>
<td>Physiologic role not established</td>
</tr>
</tbody>
</table>

Both ACTH and β-lipotropin, β-endorphin are derived from a single gene product (protein): Proopiomelanocortin (POMC).

The final processing of POMC apparently occurs in the secretory vesicle, and thus all of the products are released into the bloodstream. ACTH is the only one of these products with a clear physiological action, although β-LPH and β-endorphin have also been proposed as having a physiological role.

As noted above, the central nervous system communicates with the anterior pituitary gland by means of secretions released into the hypothalamo-hypophyseal portal system. These neurosecretions are called hypophysiotropic hormones. The known tropic hormones of this type are listed in the table on the next page. However, the amounts of these hormones released is so small that they are extremely hard to detect. Thus, others may also exist, but are yet to be discovered.
Hypophysiotropic Hormone | Amino Acids | Physiological Effects on the Pituitary
---|---|---
Corticotropin-releasing hormone (CRH) | 41 | Stimulates secretion of ACTH, β-LPH, and β-endorphin
Gonadotropin-releasing hormone (GnRH), originally called luteinizing hormone-releasing hormone (LHRH) | 10 | Stimulates secretion of FSH and LH
Growth hormone releasing hormone (GHRH) | 40 or 44 | Stimulates secretion of GH
Somatotropin release-inhibiting factor (SRIF) | 14 or 28 | Inhibits secretion of GH
Prolactin-stimulating factor (?) | ? | Stimulates prolactin secretion
Prolactin-inhibiting factor (PIF) | Dopamine | Inhibits prolactin secretion
Thyrotropin-releasing hormone | 3 | Stimulates secretion of TSH and prolactin

As noted above, the release of these tropic hormones is typically regulated through negative feedback loops. The end-product hormone released from the peripheral endocrine gland (e.g., thyroid hormones) inhibits the release of the tropic factor into the hypothalamo-hypophyseal portal system through so-called long-loop negative feedback. Furthermore, pituitary hormones inhibit the release of tropic hormones through short-loop negative feedback. It has also been proposed that high levels of the hypothalamic tropic hormones can directly inhibit their own production, through ultra-short-loop negative feedback.

For hormonal systems to function appropriately, a number of conditions must be met. First, endocrine tissue must be able to respond appropriately to negative feedback mechanisms. Sometimes pathology interferes with this homeostatic regulation. For example, tumors of the endocrine glands can cause massive overproduction of a hormone that is completely unregulated. Furthermore, the appropriate number of receptors for the hormone must be present in the appropriate tissue. In some cases, conditions such as autoimmune diseases can drastically reduce the number of peripheral receptors, thereby diminishing the response to release of a particular hormone. Similarly, intracellular signal transduction pathways can become aberrantly altered, thereby restricting the responses to hormonal release.

POSTERIOR PITUITARY HORMONES

The posterior pituitary gland secretes two small peptides whose structure is very similar: oxytocin and vasopressin. Vasopressin was first isolated from pigs, and differs from human vasopressin in having a lysine instead of an arginine residue in position 8 of the peptide chain. It is for this reason that human vasopressin is usually referred to as arginine vasopressin (AVP). Vasopressin received its name because of the ability of the hormone to induce the contraction of vascular smooth muscle. However, at much lower concentrations the hormone also promotes the reabsorption of water by renal tubules. For this reason, vasopressin is commonly known by another name: antidiuretic hormone (ADH). Oxytocin means “rapid birth,” and the hormone received this name because it serves to stimulate uterine contractility during childbirth. Furthermore, it stimulates the release of milk from mammary glands during suckling. However, oxytocin presumably has other, yet to be discovered functions, as the hormone is present in nonreproductive age women as well as men.
ADH and oxytocin are synthesized in separate neurons whose cell bodies are located in the supraoptic and paraventricular nuclei of the hypothalamus. The hormones are packaged into secretory vesicles, and transported to the nerve terminals in the posterior pituitary to await release. Because these hormones are synthesized and stored in nerve cells, their secretion is controlled in the same way as conventional neurotransmission. The neurons integrate a number of neural inputs, and if excitation is sufficient an action potential is elicited that propagates to the nerve terminal to cause hormone release. Because the hypothalamic neurons that synthesize oxytocin and vasopressin integrate a large number of neural inputs, a variety of conditions can result in hormonal release. For example, although somatic stimulation associated with suckling provides a potent excitatory drive to oxytocin-secreting neurons, other stimuli such as the sound of an infant crying can also result in the excitation of these neurons, a release of oxytocin, and the discharge of milk.

**Question for discussion:** What are the major differences between the actions of anterior and posterior pituitary hormones that require such different mechanisms to control hormonal release?

**EXAMPLES OF HORMONES, AS AN OVERVIEW OF ENDOCRINOLOGY**

During this course, we will be discussing well over 100 hormones that regulate physiological processes. As an introduction to endocrine regulation, let us consider a few of these hormones, their actions, and the conditions that stimulate and inhibit their secretion. A list of selected hormones appears on the next page. From this list, you should deduce the general types of ‘stimulators’ for hormonal secretion as well as how hormonal secretion is inhibited.
<table>
<thead>
<tr>
<th>Inhibitor of Hormone Release</th>
<th>Testosterone, estrogen, progesterone, inhibin</th>
<th>None</th>
<th>None</th>
<th>Increased sodium in plasma</th>
<th>Somatostatin; low pH in stomach</th>
<th>Sympathetic activity</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulator of Hormone Release</td>
<td>GnRH from hypothalamus</td>
<td>LH from anterior pituitary</td>
<td>Hypoxia of cells of production</td>
<td>Increased potassium in plasma, Angiotensin II</td>
<td>Peptides and amino acids in stomach lumen; enteric nervous system</td>
<td>Sympathetic nervous activity</td>
<td>None</td>
</tr>
</tbody>
</table>

**Effect**

<table>
<thead>
<tr>
<th>Tissue of Production</th>
<th>Anterior pituitary</th>
<th>Mainly Leydig cells of Testes</th>
<th>Kidney, probably tubular epithelial cells</th>
<th>Adrenal cortex</th>
<th>G cells of stomach</th>
<th>Islet of Langerhans</th>
<th>Adrenal medulla</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone</td>
<td>LH</td>
<td>Testosterone</td>
<td>Erythropoietin</td>
<td>Aldosterone</td>
<td>Gastrin</td>
<td>Insulin</td>
<td>Epinephrine</td>
</tr>
</tbody>
</table>

Stimulates Leydig cells of testes to synthesize and release testosterone; stimulates estrogen and progesterone secretion by corpus luteum; stimulates ovulation.

Production and maintenance of male sexual characteristics.

Stimulation of red blood cell formation by bone marrow.

Promotes reabsorption of sodium and excretion of potassium by tubular epithelial cells of kidney.

Stimulates acid secretion by stomach.

Enhances glucose transport by many tissues, enhances metabolism and storage of glucose.

A host of effects through binding to $\beta$-adrenergic receptors; typically a ‘fight or flight’ response.