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Excerpt
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Classification of chemical messengers

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1.1 Hormones, the brain and behavior

Neuroendocrinology is the study of how the brain controls the endocrine systems that keep us alive and able to reproduce. However, an essential and critical characteristic of this neural control of the endocrine systems is that endocrine hormones in turn have profound effects on brain function through feedback systems. Research on hormones and the brain is intensive and covers many fields: from cell and molecular biology and genetics to anatomy, physiology, pharmacology, biochemistry, medicine, psychiatry and psychology. This book will examine the interactions between hormones, the brain and behavior. Thus, the primary focus will be on how the endocrine and nervous systems affect each other to produce an integrated functional neuroendocrine system that influences physiological and behavioral responses. As preliminary background reading, students are referred to any modern text on Human Physiology (see "Further reading" at the end of this chapter).

When you hear the term "hormone," for example *steroid hormone*, you think of the endocrine glands and how their secretions influence physiological responses in the body, but this is only part of the picture. Many of the endocrine glands (although not all of them) are influenced by the pituitary gland, the so-called "master gland," and the pituitary is itself controlled by various hormones secreted from the hypothalamus, a part of the brain situated directly above the pituitary gland. The release of hypothalamic hormones is in turn regulated by neurotransmitters released from nerve cells (neurons) in the brain. Some neurotransmitters released within the brain also control behavior, and the secretion of neurotransmitters from specific nerve cells can be modulated by the level of specific endocrine hormones in the circulation. This is called hormone feedback. Thus, neurotransmitter release influences both hormones and behavior and, in turn, hormones regulate the release of neurotransmitters. This interaction between hormones, the brain and behavior involves a wide variety of chemical messengers which are described in this chapter.

This chapter provides an introduction to the chemical messengers found in the neuroendocrine system. Later chapters describe the endocrine glands and their hormones (Chapter 2), the pituitary gland and its hormones (Chapter 3) and the regulation of the pituitary gland by hypothalamic hormones (Chapter 4). Chapter 5 outlines the role of neurotransmitters in communicating between nerve cells and Chapter 6 discusses neurotransmitter control of hypothalamic, pituitary and other hormones. The regulation of hormone synthesis, transport, storage, release and deactivation is described in Chapter 7. Hormones from the endocrine glands, pituitary gland and hypothalamus influence each other through feedback mechanisms, which are described in Chapter 8. Hormones act on target cells in the body and the brain that have specific hormone recognition sites (*receptors*). The nature of steroid and thyroid hormone receptors is discussed in Chapter 9 and the receptors for peptide hormones and neurotransmitters, which function by activating intracellular second messenger signals in their target cells, are described in Chapter 10. In the brain, hormones influence the release of both neurotransmitters and hypothalamic hormones by their action on neural target cells. The brain is also influenced by a number of newly discovered substances called *neuropeptides*, which are introduced in Chapter 11. Neuropeptides are important because they can act as *neurotransmitters* to modify neural activity or as *neuromodulators* to influence the synthesis, storage, release and action of other neurotransmitters in modifying brain function (Chapter 12). The cells of the immune system also produce chemical messengers called cytokines that interact with the neural and endocrine systems as described in Chapter 13. When hormones, neuropeptides or cytokines alter the synthesis and release of neurotransmitters in the brain, one result is a change in behavior. Methods for the study of hormones and behavior are discussed in Chapter 14, and current developments in behavioral neuroendocrinology, as well as a historical overview, are given in Chapter 15.

The neuroendocrine system, therefore, involves a network of hormone-brain-behavior interactions and an example is depicted in Figure 1.1 (Hyman 2009). This figure illustrates how adrenal steroid hormones (*glucocorticoids*) are involved in our response to stress. The perception of an environmental stimulus such as a light, odour, sound or touch occurs through the sense organs and their neural connections to the brain. These stimuli can be interpreted as physical stressors, sexual stimuli, etc. by the cerebral cortex and other brain areas that influence the neuroendocrine system. Two different responses then occur. There is a rapid neuromuscular response, resulting in an immediate behavioral change: for example, you see a truck coming and you jump out of the way. This is accompanied by complex neuroendocrine changes. Your hypothalamic-pituitary-adrenal response to the oncoming truck involves an immediate (seconds to minutes) release of many different hormones which circulate through the bloodstream to stimulate their target cells in the heart, adrenal glands, liver, skeletal muscles, adipose tissue and, of course, the brain. When the target cell is stimulated, it undergoes a physiological change caused by the hormonal action. The hormones released into circulation then exert feedback to the hypothalamus and pituitary gland, to alter further hormone release. Finally, when the brain is a target for hormonal action, the result may be a behavioral as well as a physiological change.

1.2 The body's three communication systems

The body has three different communication systems: the nervous system, the endocrine system and the immune system, each of which uses its own types of chemical messenger. Nerve cells communicate through the release of neurotransmitters; endocrine glands secrete hormones, and the immune system operates through the release of cytokines. These three systems are not independent; each one interacts with the other two, as outlined in Figure 1.2 (Glaser and Kiecolt-Glaser 2005).

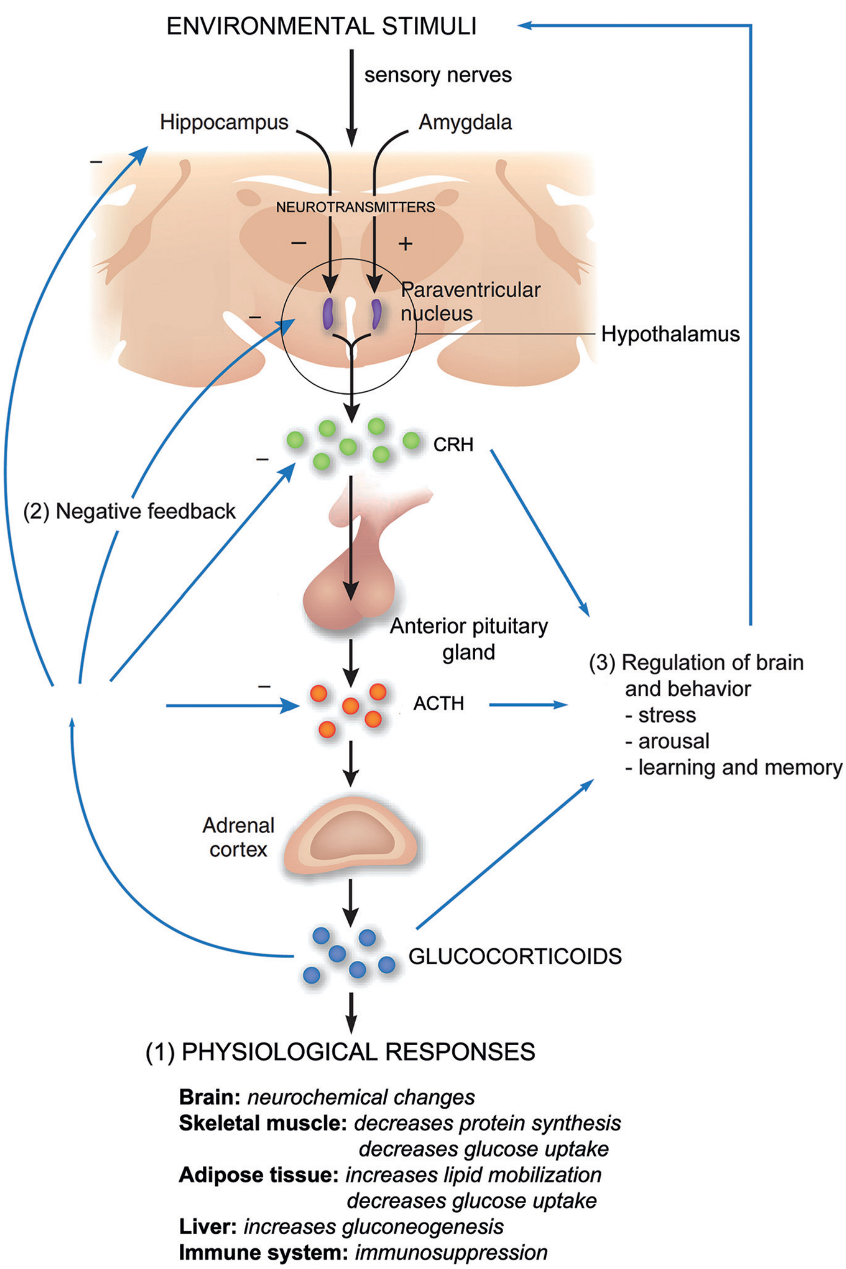

Figure 1.1 The interaction between hormones and the brain
Environmental stimuli influence the brain through sensory nerves and the brain regulates behavior and hormone secretion through the release of neurotransmitters that stimulate nerve impulses. The hormones released from the hypothalamus, pituitary gland and other endocrine glands when the neuroendocrine system is activated stimulate: (1) physiological responses in target cells in the brain and body; (2) feedback regulation of hypothalamic and pituitary hormone release; and (3) brain and behavioral responses through their action on neurotransmitter and neuropeptide release from neurons in the brain. The example used here is the hypothalamic-pituitary-adrenal response to an environmental stressor.

Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone. Reproduced with permission (Hyman 2009).

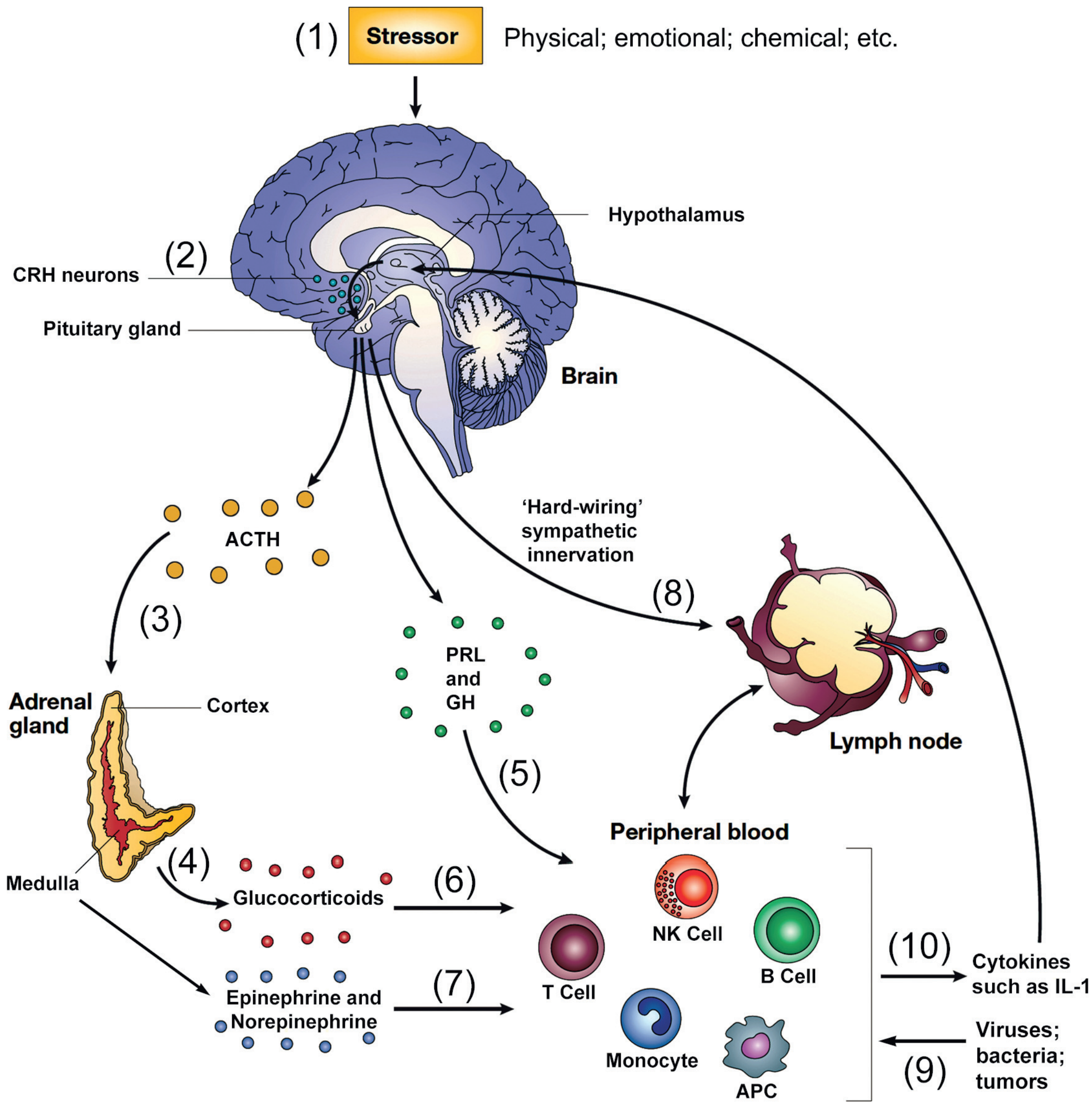

Figure 1.2 The body's three communication systems do not act independently

The brain and nervous system influence the neuroendocrine and immune systems, which also influence each other and the brain. This example shows that cognitive stimuli (stressors (1)) activate the neuroendocrine system through the brain and nervous system (e.g. through hypothalamic activation of CRH neurons (2)). The secretion of CRH from hypothalamic neurons stimulates the anterior pituitary gland to release ACTH (3), which in turn acts on the adrenal cortex to release glucocorticoids (4). Pituitary hormones such as prolactin (PRL) and GH (5), as well as glucocorticoids (6), also influence cells of the immune system.

Autonomic neural activity is also regulated as a result of stressors (1). For example, the sympathetic branch of the autonomic nervous system induces release of epinephrine and norepinephrine from the adrenal medulla (7). Other branches of the autonomic system stimulate cells of the immune system to release cytokines (8). Note that non-cognitive stimuli such as viruses and bacteria can directly activate cells of the immune system (9) and the resulting release of cytokines (10) activates the neuroendocrine system.

Abbreviations: ACTH, adrenocorticotropic hormone; APC, antigen-presenting cell; CRH, corticotropin-releasing hormone; GH, growth hormone; IL-1, interleukin-1; NK, natural killer; PRL, prolactin. Reproduced with permission (Glaser and Kiecolt-Glaser 2005).

Because these systems interact, they are often referred to as the neuroendocrine, neuroimmune or neuroimmunoendocrine systems. To designate the influence of these systems on behavior, the terms *psychoneuroendocrinology* (Smythies 1976) and *psychoneuroimmunology* (http://en.wikipedia.org/wiki/Psychoneuroimmunology) have been coined. These important fields of science have specific journals devoted to them.

As shown in Figure 1.2, the nervous system controls the release of hormones that can influence the release of cytokines from the immune system. In turn, hormones and other chemical messengers modulate the activity of both the nervous system and the immune system. Likewise, the immune system can modulate both neural activity and the release of hormones by the release of cytokines. While cognitive-sensory stimuli influence neural, immune and endocrine activity through the brain and nervous system, non-cognitive stimuli, such as bacteria and viruses, influence these systems through their action on the immune system.

1.3 Methods of communication between cells

As shown in Figure 1.3, hormones and other chemical signals may communicate with their target cells through *endocrine, paracrine, autocrine* and *neuroendocrine* mechanisms. These are compared with neurochemical signaling between neurons, sometimes called *neurocrine.* A special case is when the signal is not released from the cell but interacts with receptors *inside* the cell; this is termed *intracrine* communication.

1.3.1 Endocrine communication

Endocrine cells release their hormones into the bloodstream and these hormones then travel via the circulation to distant target cells. For example, thyroid-stimulating hormone (TSH) is released from the pituitary gland and travels through the bloodstream to stimulate its target cells in the thyroid gland (see Figure 6.6).

1.3.2 Paracrine communication

Endocrine cells also release hormones that act on adjacent cells. These hormones may diffuse from one cell to the next, or go into the bloodstream, but travel only a very short distance. Paracrine secretion is, therefore, a localized hormone action. This happens, for example, in the ovaries. In order to produce the sex hormone estradiol, granulosa cells must first take up androgen which is released from the adjacent thecal cells. The androgen, for example, androstenedione, is then converted to estradiol (see Widmaier *et al.* 2010). The target cell is located immediately adjacent to the hormone-secreting cell, resulting in a localized chemical communication within a particular tissue or organ. Paracrine secretion is also important in the immune system and nervous system (see section 1.3.3).

1.3.3 Neurocrine communication

A special type of *paracrine* communication is that between cells in the nervous system. Here, nerve cells (neurons) secrete neurotransmitters, such as acetylcholine, that travel

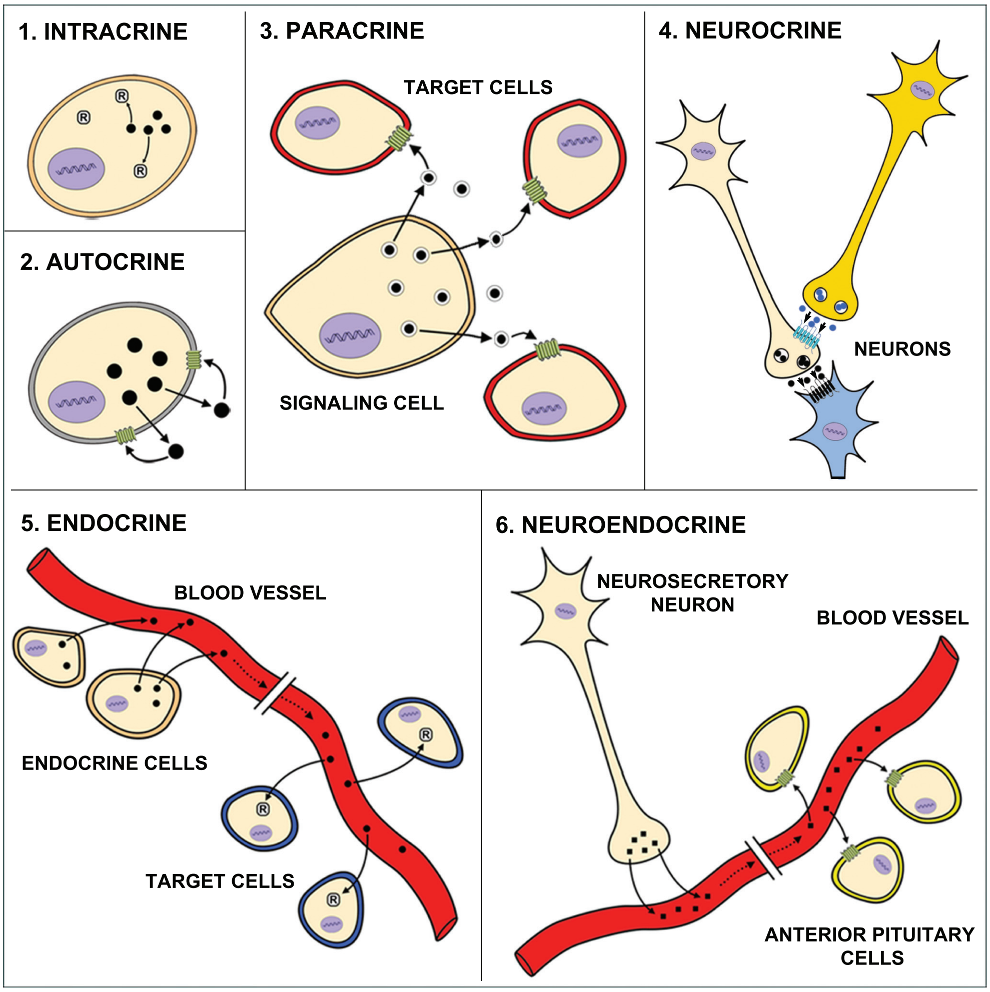

Figure 1.3 Methods of communication between cells of the (neuro)endocrine system
In *intracrine* communication (1) hormonal messengers, either synthesized in the same cell or imported from the bloodstream, act at intracellular receptors. In *autocrine* communication (2), hormones act on the cells that release them. In *paracrine* communication (3), hormones act on adjacent cells such as occurs in the testes, gastrointestinal tract and brain. A special form of paracrine signaling, sometimes called *neurocrine* (4), is the close-range signaling that occurs between nerve cells (neurons). *Endocrine* communication (5) occurs when hormones are released into the bloodstream and act on cells at distant sites throughout the body. *Neuroendocrine* communication (6) occurs when neuropeptides are released from presynaptic cells into the synapse and act on receptors of postsynaptic cells in the central and peripheral nervous systems. Neuroendocrine secretion also involves the release of neurohormones from neurosecretory neurons in the hypothalamus and adrenal medulla. Copyright P. M. H. Wilkinson.

ultra-short distances across a synapse to either stimulate or inhibit other postsynaptic neurons (see Chapter 5). Another example is when neuropeptides are secreted from neurons in the brain. These behave as neuromodulators by regulating the sensitivity of other cells to stimulation (see Chapter 11).

1.3.4 Autocrine communication

This is a modified form of paracrine secretion in which a cell releases a hormone or neurotransmitter that then has a direct feedback effect on the secretory cell itself. This is referred to as autocrine action. A specific example of autocrine communication would be a neurotransmitter acting presynaptically to modify its own secretion.

1.3.5 Neuroendocrine communication

Neuroendocrine (neurosecretory) cells are neurons that release peptide hormones either into the peripheral circulatory system, so that they can stimulate distant target cells (e.g. the release of oxytocin by the posterior pituitary to stimulate targets cells in the uterus – see Figure 6.10) or into the hypothalamic portal vessels to induce the release of pituitary hormones (e.g. gonadotropin-releasing hormone [GnRH] released from the hypothalamus to stimulate the release of luteinizing hormone from the anterior pituitary – see Figure 6.7).

1.3.6 Intracrine signaling

Some hormones, such as the steroid hormones estradiol and testosterone, are biosynthesized in the gonads, transported in the bloodstream, and act via receptors that are inside the target cells (see Chapter 9). However, some tissues, such as vagina, bone and prostate, possess estradiol and testosterone receptors, but are also able to biosynthesize these steroids within the cell without them being secreted. Thus, they can bind to receptors in the same cell and exert so-called *intracrine* signaling (Labrie *et al.* 2001). Other examples include growth factors, such as fibroblast growth factor (FGF), which are produced inside cells and bind directly to intracellular receptors, *without actually leaving the cell*, perhaps as a mechanism for control of cell proliferation.

1.4 Types of chemical messenger

The classification of chemical messengers is a constantly changing endeavor as new substances and new functions for known substances are continuously being discovered.

1.4.1 Phytohormones

Phytohormones are chemical messengers such as auxins, kinins, gibberellins and other growth regulators produced by the higher plants. Although this book is not directly concerned with the actions of phytohormones, they should interest us for two reasons. First, many phytohormones are similar to known mammalian hormones and neurotransmitters and may thus be important in understanding the evolution of the neuroendocrine system. Second, some phytohormones are used as drugs that can influence the human neuroendocrine system. Thus, plant substances such as muscarine, nicotine and morphine stimulate highly specific receptors on mammalian target cells, while atropine, ergocornine and strychnine block target cell receptors, preventing their response to hormones and neurotransmitters. In some cases, the same chemical may be found in both plants and

Table 1.1 Types of chemical messenger

Phytohormones: plant hormones – kinins, auxins, gibberellins, etc. *"True" hormones*: these are (a) chemical messengers which are (b) synthesized in ductless (endocrine) glands and (c) secreted into the bloodstream. They (d) act on specific target cell receptors and (e) exert specific physiological (biochemical) regulatory actions in the target cells. They can be steroid hormones (e.g. estradiol and testosterone) or peptide hormones (e.g. insulin or growth hormone).
Neurohormones: hormones that are released by hypothalamic neurosecretory cells (neurons) via the posterior pituitary into the circulation (e.g. oxytocin and vasopressin) or via the portal system, into the anterior pituitary (the so-called hypothalamic releasing/inhibiting hormones).
Neurotransmitters: these are released by presynaptic nerve cells into a synapse (e.g. acetylcholine, dopamine, norepinephrine, etc.), where they stimulate receptors on postsynaptic nerve cells.
Pheromones: these are (a) volatile chemical messengers that are (b) synthesized in exocrine (duct) glands and (c) secreted into the environment. They (d) act on other individuals, usually of the same species, through olfactory (smell) or gustatory (taste) receptors and (e) alter behavior (releaser effects) or the neuroendocrine system (primer effects).
Parahormones: hormone-like substances which are not necessarily produced in endocrine glands (e.g. histamine, prostaglandins, leukotrienes, vitamin D). Prostaglandins and leukotrienes, for example, are generated locally during a tissue inflammatory response and act in a paracrine fashion.
Prohormones: these can be (a) large peptide molecules that may be processed into single or multiple hormones (e.g. pituitary beta-lipotropin is converted to β-endorphin (β-END) and adrenocorticotropic hormone (ACTH), or (b) steroid hormones converted to other bioactive steroids (e.g. testosterone to estradiol).
Growth factors: hormone-like substances which promote growth of body or brain tissue; e.g. nerve growth factor (NGF) or epidermal growth factor (EGF).
Cytokines. hormone-like factors released from lymphocytes, macrophages and other cells of the immune system that regulate the activity of cells of the immune system (e.g. interferon-γ and the interleukins).
Adipokines: one of the largest endocrine glands in the body is our fat tissue, which secretes a large number of hormone-like substances, such as leptin. Leptin regulates appetite and body weight. Some adipokines, such as interleukins, are also cytokines.
Vitamins: chemicals that regulate metabolism, growth and development in the body. Vitamin D for example, is synthesized in the body and has many hormone-like properties. If not produced in sufficient quantities, it must be taken as a dietary supplement in order to maintain bone strength.

animals. For example, abscisic acid – a phytohormone that causes leaves and fruit to fall from trees – is also found in human granulocytes, perhaps acting as part of the immune system (Minorsky 2002).

1.4.2 Hormones

A hormone is defined as: (a) a chemical messenger which is biologically effective in minute quantities (nanomolar 10^{-9} M, or picomolar 10^{-12} M); (b) synthesized in a ductless or endocrine gland; (c) secreted into the circulatory system, and transported through the body in the blood to (d) act on receptors on specific target cells located at a distance from the site of synthesis by (e) exerting a specific physiological or biochemical regulatory action on the target cell.

Chemical messenger

Hormones are chemical messengers that regulate the physiological actions of their target cells, but not all physiological regulators are hormones. For example, there are a number of non-hormonal chemicals, such as carbon dioxide, nitric oxide, glucose (blood sugar), histamine and the prostaglandins, which also regulate the physiological actions of their target cells.

Hormones are effective in minute quantities, although the physiological concentrations vary, depending on the hormone. Normally, the hypothalamic-releasing hormones (e.g. thyrotropin-releasing hormone, TRH; corticotropin-releasing hormone, CRH) are secreted in very small quantities (femtograms, 10^{-15} g). Pituitary hormones are released in greater quantities (picograms, 10^{-12} g) and gonadal, adrenal and thyroid hormones are released in much larger quantities (nanograms, 10^{-9} g). Modern assay technology has enabled these hormones to be detected and quantified on a routine clinical basis.

Biosynthesis in an endocrine gland

Although hormones are synthesized in endocrine glands, some hormone-like chemicals are produced in other locations. The production of angiotensin I, for example, occurs in the bloodstream, not in an endocrine gland. Neurohormones (e.g. hypothalamic-releasing hormones, oxytocin and vasopressin) are synthesized in neurosecretory cells which are modified neurons. Growth factors such as somatomedin and nerve growth factor act to promote tissue growth, but are not synthesized in endocrine glands. Likewise, the lymphokines, which have hormone-like activity, are synthesized by lymphocytes.

Some hormones are synthesized in a number of locations. Insulin, for example, is synthesized in both the pancreatic islets and in the brain and somatostatin is produced in both the pancreas and the brain. Estradiol is synthesized in the ovaries, testes, adrenal cortex, placenta, brain and by tumor cells. Peptides, such as somatostatin, are called hormones when they are secreted from endocrine glands, but if they are produced by neurons in the brain, they are called neuropeptides. Finally, some hormones such as adrenocorticotropin (ACTH) are secreted from the pituitary gland, from lung cancer cells and from lymphocytes and other cells of the mammalian and non-mammalian immune systems. As we will see in Chapter 12, hormones such as ACTH can also be synthesized in the brain and act as neuropeptides.

Secreted into the bloodstream

The traditional definition of a hormone is that it is secreted into the bloodstream and transported to its target cells through the circulatory system. But as we have seen already, many chemical messengers are not secreted into the bloodstream; that is, hormones can activate the cell adjacent to the one that releases them (*paracrine* action) or even the same cell that releases them (*autocrine* action). Neurotransmitters and neuropeptides are secreted from neurons into a synapse (i.e. the junction between two nerve cells). Neurohormones, neuropeptides and neurotransmitters may also be transported by the cerebrospinal fluid (CSF), as well as by the circulatory system, and the small quantities which enter the blood are quickly degraded. Pheromones are released into the air by one individual to act on another individual.

Act on specific target cells located at a distance from the site of synthesis

Although hormones are defined as acting on specific target cells, some hormones act on several different cell types in the body, rather than on a single and specific cell type. For example, growth hormone affects a variety of cells – such as liver, muscle and fat tissue – so it is hard to say that there is a specific target cell for this hormone. Likewise, glucocorticoids such as cortisol act on virtually every type of cell in the body.

Hormones are also defined as acting at target cells located at a distance from the site of synthesis, but how large is this distance? Hypothalamic hormones travel only a short distance down the portal venous system to the anterior pituitary gland. Paracrine hormones influence the very next cell. Autocrine hormones act on the same cell that secretes them. On the other hand, pituitary hormones such as luteinizing hormone (LH) influence the gonads, so they travel a long distance through the bloodstream. In turn, gonadal hormones such as testosterone influence the brain by traveling through the whole circulatory system before reaching their target cells.

Specific physiological actions

Although hormones are defined as having a specific action at their target cell, this action may vary according to the type of target cell stimulated. For example, prolactin stimulates the production of milk in the breast, and this is an example of a specific hormonal function. Estradiol, on the other hand, can increase tissue growth, such as in bone, or in the uterus during pregnancy, and it can increase the sensitivity of the pituitary to stimulation by gonadotropin-releasing hormone (GnRH) during the menstrual cycle. Moreover, some hormones can interact with multiple receptor types such that they have different functions in different target cells. For example, norepinephrine (sometimes called noradrenaline) released from the adrenal medulla can bind to either α-adrenergic or β-adrenergic receptors on target cells in muscle tissue and the physiological action stimulated may differ depending on which receptor is activated (see Chapter 10). Heart rate is increased via β-adrenergic receptor stimulation, whereas bronchoconstriction is mediated by α-adrenergic receptors. In contrast, many different hormones, no matter what their target cell, induce the same signaling response; that is, an increase in intracellular cyclic adenosine monophosphate (cAMP) production.

1.4.3 Neurohormones

A neurohormone differs from a "true" hormone because it is synthesized and released from a neurosecretory cell, which is a modified neuron. Two of the best studied neurohormones are oxytocin and vasopressin. These are hormones manufactured in the brain by hypothalamic neurosecretory cells, although they are stored and released from nerve terminals located in the posterior pituitary gland. The releasing hormones of the hypothalamus, such as corticotropin-releasing hormone (CRH) and gonadotropin-releasing hormone (GnRH), are also neurohormones. Chapters 3 and 4 will describe the