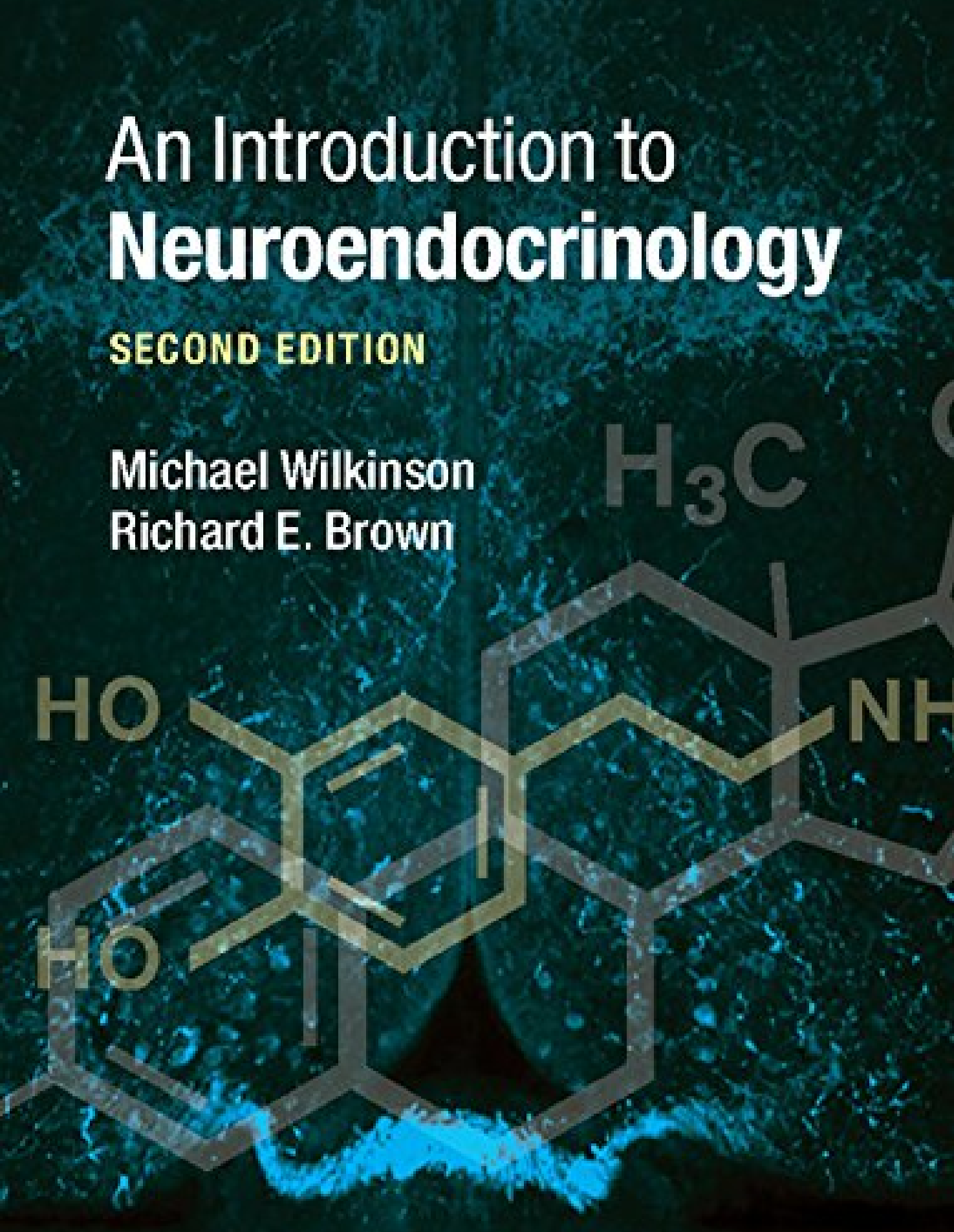
An Introduction to Neuroendocrinology

SECOND EDITION

Michael Wilkinson
Richard E. Brown



An Introduction to Neuroendocrinology

Second Edition

How does the brain regulate sexual behavior, or control our body weight? How do we cope with stress? Addressing these questions and many more besides, this thoroughly revised new edition reflects the significant advances that have been made in the study of neuroendocrinology over the last 20 years.

The text examines the importance of the hypothalamus in regulating hormone secretion from the endocrine glands, describing novel sites of hormone release, including bone, heart, skeletal muscle, and liver. The role of steroid hormone, neurotransmitter and peptide receptors, and the molecular responses of target tissues, is integrated into the discussion of the neuroendocrine brain, especially through changes in gene expression. Particular attention is attached to neuropeptides, including their profound influence on behavior.

Complete with new full-color figures throughout, along with review and essay questions for each chapter, this is an ideal resource for undergraduate and graduate students of neuroscience, psychology, biology, and physiology.

Michael Wilkinson has 40 years of experience in teaching neuroscience and neuroendocrinology to undergraduate and graduate students as a Professor in the Department of Obstetrics and Gynaecology and IWK Health Centre, Dalhousie University, Halifax, Canada. His research laboratory has focused on neurodevelopmental aspects of female reproduction with a specific interest in the neuroendocrine regulation of hypothalamic function, including the impact of sex hormones on sleep.

Richard E. Brown is a University Research Professor in the Department of Psychology and Neuroscience at Dalhousie University. He has taught courses on hormones and behavior, measuring behavior, and the neurobiology of learning and memory for more than 35 years. His research is on mouse models of Alzheimer's Disease, Fragile X Syndrome, ADHD, and other neurological disorders. He is currently examining the age-related hormonal changes in transgenic Alzheimer's mice.

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This book is dedicated, first, to the more than 2,000 Dalhousie University students who were enrolled in the "Hormones and Behavior" undergraduate course and who were the original inspiration for writing the book. Many of them provided critical comments on early drafts of the first edition.

Second, one of us (M. W.) acknowledges the mentorship of the late Professor Kurt B. Ruf, a neuroendocrinologist and friend.

CONTENTS

PREFACE TO THE SECOND EDITION

In this second edition of *An Introduction to Neuroendocrinology*, we have rewritten and greatly extended the original content. The revised text includes entirely new reference lists and a complete new set of illustrations. The book reflects the many advances that have occurred in the study of neuroendocrinology during the past 20 years. Nevertheless, and although the text is based largely on modern references, our primary aim is to provide an introductory description of mammalian neuroendocrine control systems. Several books are available that cover this topical and clinically relevant field, but, although valuable, these tend to be advanced texts of the edited, multi-author type. Our book is designed to provide the basic principles necessary to understand how the brain controls, and responds to, the endocrine hormones. It will be suitable for a variety of different students and especially those who might not have been previously exposed to a focused course in neuroendocrinology. Thus, students in psychology, biology and science should be able to master much of the basic material. However, the book is also highly appropriate for honors students and first-year graduate students in physiology, anatomy, neuroscience and medicine. This book is therefore designed for students in two levels of classes: introductory classes, in which all of the material will be new to the student, and more advanced classes, in which the students will be familiar with many of the terms and concepts through courses in biology, physiology, psychology or neuroscience, but who have not studied neuroendocrinology as an integrated discipline.

This book offers an overall outline of the neuroendocrine system and will provide the vocabulary necessary to understand the interaction between hormones and the brain. In addition, we provide a concise description of those topics that must underpin any attempt to learn, and to teach, neuroendocrinology. For example, there are chapters on basic neuroscience (neurotransmitters and neuropeptides), the physiology of the endocrine glands (hormones), receptors and receptor signaling mechanisms (e.g. G proteins; nuclear receptors), hormone assay and gene expression techniques (e.g. ELISA; *in situ* hybridization) and a description of the immune system, with particular emphasis on the integration of immune and neuroendocrine pathways. This basic information is also essential to understand the profound effects of hormones on behavior, described in Chapter 14. Once this material is mastered, the study of how hormones influence developmental neural processes and behavior will be easier. Moreover, we have included throughout the book references to the clinical relevance of many topics; for example, the influence of neuropeptides in the control of body weight and obesity. However, this book focuses primarily on the neural actions of hormones, and many of the peripheral physiological actions of hormones, such as regulation of metabolism, water balance, growth, and the regulation of calcium, sodium and potassium levels, which are the focus of traditional endocrinology texts, are referred to only in reference to their importance in the neuroendocrine system.

The introductory (second- or third-year undergraduate) student can be expected to follow the material in this book at the level presented. To help in this, review/study

questions are given at the end of each chapter. These should be treated as practice examination questions and answered after each chapter is completed. For further detailed information on the topics covered in each chapter, all students can consult selected references provided in the text. Additional references under "Further reading" are also included at the end of each chapter and these will be particularly useful to the more advanced student. The book will be especially relevant for more advanced (honors and graduate) students who can use this book as an introductory account of the subject matter covered in each chapter. These students may then take advantage of the many references cited in each chapter to provide current and relevant information on each topic. The essay questions at the end of each chapter also serve to provide topics for discussion, analysis and directed research papers for the advanced student.

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Finally, thanks are due to Megan Waddington of Cambridge University Press for her patience in awaiting the delivery of this manuscript.

ABBREVIATIONS

IIIv	third ventricle
2-AG	2-arachidinoyl glycerol
5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine (serotonin)
5-HTP	5-hydroxytryptophan
6-OHDA	6-hydroxy-dopamine
AC	adenyl cyclase
ACh	acetylcholine
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone (vasopressin)
ADHD	attention deficit hyperactivity disorder
AEA	anandamide
AgRP	agouti-related protein
AH	anterior hypothalamus
AHA	anterior hypothalamic area
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
AMYG	amygdala
ANP	atrial natriuretic peptide
ANS	autonomic nervous system
AP	area postrema
APC	antigen presenting cell
APUD	amine precursor uptake and decarboxylation
AR	androgen receptor
ARC	arcuate nucleus
AT	angiotensin
ATP	adenosine triphosphate
AVP	arginine vasopressin
AVPV	anteroventral periventricular nucleus
β2-AR	β2-adrenergic receptor
β-END	β-endorphin
β-Gal-ir	β-Galactosidase immunoreactivity
BBB	blood-brain barrier
BDNF	brain-derived neurotrophic factor
BLA	basolateral amygdala
BNP	B-type natriuretic peptide
Ca^{2+}	calcium ion
CAH	congenital adrenal hyperplasia
cAMP	cyclic adenosine monophosphate
CART	cocaine- and amphetamine-regulated transcript
cGMP	cyclic guanosine monophosphate
CB1	cannabinoid receptor 1
CBG	corticosteroid binding globulin (transcortin)
CCK	cholecystokinin
CCK-KO	CCK knockouts
CGRP	calcitonin gene related peptide
ChAT	choline acetyltransferase
CL	centrolateral thalamus
Cl^-	chloride ion
CLIP	corticotropin-like intermediate lobe peptide
CM	centromedial thalamus
CNS	central nervous system
COMT	catechol o-methyl transferase
CP	caudate/putamen
CREB	cAMP responsive element binding protein
CRF	corticotropin-releasing factor (also called CRH)
CRH	corticotropin-releasing hormone (also called CRF)
CSF	cerebrospinal fluid
CVO	circumventricular organs
D	diestrus
D2R	dopamine 2 receptor
D3	diestrus 3
DA	dopamine
DAG	diacylglycerol
DBD	DNA binding domain
DBH	dopamine beta-hydroxylase
DG	dentate gyrus
DHEA	dehydroepiandrosterone
DHT	dihydrotestosterone
dISON	dorsolateral supraoptic nucleus
DMN	dorsomedial hypothalamic nucleus
DMT	dimethyltryptamine
DNA	deoxyribonucleic acid

DNES	Diffuse Neuroendocrine System
DYN	dynorphin
E	estradiol
EDC	endocrine disrupting chemicals
EGF	epidermal growth factor
EGL	external granule cell layer
EL	ejaculation latency
ELISA	enzyme-linked immunosorbent assay
ENK	enkephalin
ENS	enteric nervous system
EOP	endogenous opioid peptide
EPO	erythropoietin
ER	endoplasmic reticulum
ER	estrogen receptor
ERE	estrogen response element
FGF	fibroblast growth factor
fMRI	functional magnetic resonance imaging
FS	folliculostellate
FSH	follicle-stimulating hormone
FSH-RH	follicle-stimulating hormone-releasing hormone
FX	fornix
G	granule cells
G-CSF	granulocyte colony stimulating factor
GABA	gamma-aminobutyric acid
GABA-T	GABA transaminase
GAD	glutamic acid decarboxylase
GDNF	glial-derived neurotrophic factor
GDP	guanosine diphosphate
GFP	green fluorescent protein
GH	growth hormone
GHRH	growth hormone releasing hormone
GH-RIH	growth hormone release inhibiting hormone (see SOM)
GI	gastrointestinal
G_i	inhibitory G protein
GIP	gastrin inhibitory peptide
GLP-1	glucagon-like peptide-1
GLP-2	glucagon-like peptide-2
Glu	glutamate
GM-CSF	granulocyte-macrophage colony stimulating factor
GnIH	gonadotropin inhibitory hormone
GnRH	gonadotropin-releasing hormone
GPR54	G-protein-coupled receptor 54
GR	glucocorticoid receptor
GRE	glucocorticoid response element
G_S	stimulatory G protein
GTF	general transcription factor
GTP	guanosine triphosphate
HBD	hormone binding domain
HCG	human chorionic gonadotropin
HCS	human chorionic somatomammotropin
HDC	histidine decarboxylase
HFD	high fat diet
HGP	hepatic glucose production
H-P-A	hypothalamic-pituitary-adrenal
HPL	human placental lactogen
HPLC	high performance liquid chromatography
HRE	hormone response element
HRT	hormone replacement therapy
HSP	heat shock protein
HVA	homovanillic acid
ICo	nucleus intercollicularis
IF	intromission frequency
IFNγ	interferon γ
I_g	immunoglobulin
IGF	insulin-like growth factor; somatomedin
IGFBP	insulin-like growth factor binding protein
IGL	internal granule cell layer
III	inter-intromission interval
IL	interleukin
IL	intromission latency
lMAN	lateral magnocellular nucleus of the anterior nidopallium
IP3	inositol triphosphate
iR	ion channel
IRS-1	insulin receptor substrate 1
JAK	janus kinase
K^+	potassium ion
K_P	kisspeptin
LH	luteinizing hormone (also lateral hypothalamus)

LHRH	luteinizing hormone releasing hormone
LPH	lipotropic hormone (also β-lipotropin)
LSD	lysergic acid diethylamide
M	muscarinic
MAO	monoamine oxidase
MBH	mediobasal hypothalamus
MC	melanocortin
M-CSF	macrophage colony stimulating factor
MD	dorsomedial thalamus
ME	median eminence
MET	metestrus
mf	mossy fibers
MF	mount frequency
mGluR	metabotropic glutamate receptor
MHC	major histocompatibility complex
MHPG	3-methoxy-4-hydroxyphenylglycol
mIU	milli international units
ML	mount latency
ML	molecular layer
MMGB	medial geniculate body
MOE	main olfactory epithelium
MPOA	medial preoptic area
mR	metabotropic membrane receptor
MR	mineralocorticoid receptor
MRF	midbrain reticular formation
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
α-MSH	α-melanocyte-stimulating hormone
MSH-RF	melanocyte-stimulating hormone – releasing factor
MSH-RH	melanocyte-stimulating hormone – releasing hormone
MSH-RIF	melanocyte-stimulating hormone – release-inhibiting factor
MSH-RIH	melanocyte-stimulating hormone – release-inhibiting hormone
MT	melatonin
MUA	multiple unit activity
NA	noradrenaline (also norepinephrine, NE)
Na^+	sodium ion
NE	norepinephrine (also noradrenaline, NA)
NGF	nerve growth factor
NK	natural killer cell
NKT	natural killer T cell
NMDA	N-methyl-D-aspartate
NO	nitric oxide
NOS	nitric oxide synthase
NP	neurophysin
NPY	neuropeptide Y
NSF	N-ethylmaleimide sensitive factor
NT	neurotransmitter
NTD	amino terminal domain
NTS	nucleus tractus solitarius
nXIIts	tracheosyringeal portion of the nucleus hypoglossus
OB	olfactory bulb
OT	oxytocin
ORL1	opioid receptor-like receptor
OTR	oxytocin receptor
OVLT	organum vasculosum of the lamina(e) terminalis
OXM	oxyntomodulin
OXY	oxytocin
P	progesterone (also Purkinje cells)
PACAP	pituitary adenylate cyclase-activating polypeptide
PC	proprotein convertase
PCP	phencyclidine
PCR	polymerase chain reaction
pCREB	phosphorylated CREB
PEI	post-ejaculatory interval
PeN	anterior periventricular nucleus
PENK	preproenkephalin
PET	positron emission tomography
pf	parallel fibers
PFA	perifornical area
PGE2	prostaglandin E2
PH	posterior hypothalamus
PI3K	phosphoinositide 3 kinase
PIF	prolactin releasing inhibiting factor
PIP2	phosphatidylinositol diphosphate
PIR	piriform cortex
PKA	protein kinase A
PL	placental lactogen
PLC	phospholipase C
PNS	parasympathetic nervous system
POA	preoptic area
POL	RNA polymerase
POMC	pro-opiomelanocortin

PP	pancreatic polypeptide
PR	progesterone receptor
PRF	prolactin releasing factor
PRH	prolactin-releasing hormone
PRL	prolactin
PRO	proestrus
PrRP	prolactin-releasing peptide
PTH	parathyroid hormone
PTSD	post-traumatic stress disorder
PV	periventricular nucleus
PVN	paraventricular nucleus
PYY	peptide YY
RA	robust nucleus of the arcopallium
RER	rough endoplasmic reticulum
RSP	retrosplenial cortex
SC	subcutaneous
SCN	suprachiasmatic nucleus
SDN	sexually dimorphic nucleus
SEM	standard error of the mean
SHBG	sex hormone binding globulin
SNAP	soluble SNF attachment proteins
SNARE	SNAP receptor protein
SNB	spinal nucleus of the bulbocavernosus
SNS	sympathetic nervous system
SOCS	suppressor of cytokine signaling
SOM	somatostatin
SON	supraoptic nucleus
SP	Substance P
SS	somatosensory cortex
SST	somatostatin receptor
STAT	signal transducer and activator of transcription / signal transduction and transcription
T	testosterone
T3	triiodothyronine
T4	thyroxine
TBG	thyroid hormone binding globulin
T_C	cytotoxic T cell
TF5	thymosin fraction 5
TGFα	transforming growth factor α
TGFβ1	transforming growth factor β1
TH	tyrosine hydroxylase
T_H	helper T cell
THC	tetrahydrocannabinol
TIDA	tuberoinfundibular DA
TNFα	tumor necrosis factor α
TR	thyroid hormone receptors
TRF	thyrotropin (TSH) releasing factor (also TRH)
TRH	thyroid hormone releasing hormone
trk	tyrosine receptor kinase
T_S	suppressor T cell
TSH	thyroid-stimulating hormone
TSHR	TSH receptor
TSH-RH	thyroid-stimulating hormone-releasing hormone (TRH)
VEGF	vascular endothelial growth factor
VIP	vasoactive intestinal polypeptide
vmSON	ventromedial supraoptic nucleus
VMH	ventromedial hypothalamic nucleus
VMN	ventromedial nucleus of hypothalamus
VNO	vomeronasal organ
VP	vasopressin
WAT	white adipose tissue (fat)

Classification of chemical messengers

1

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).

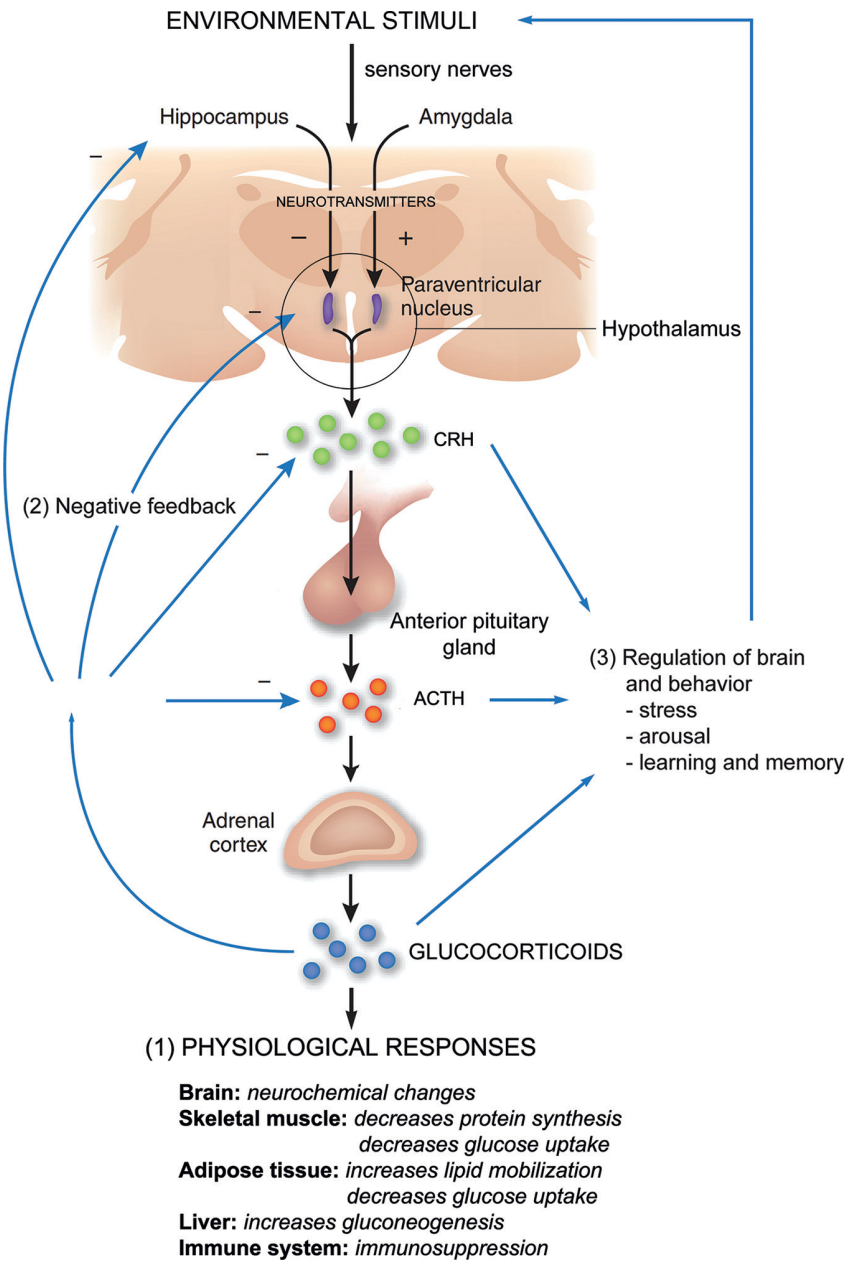

Figure 1.1 The interaction between hormones and the brain

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).

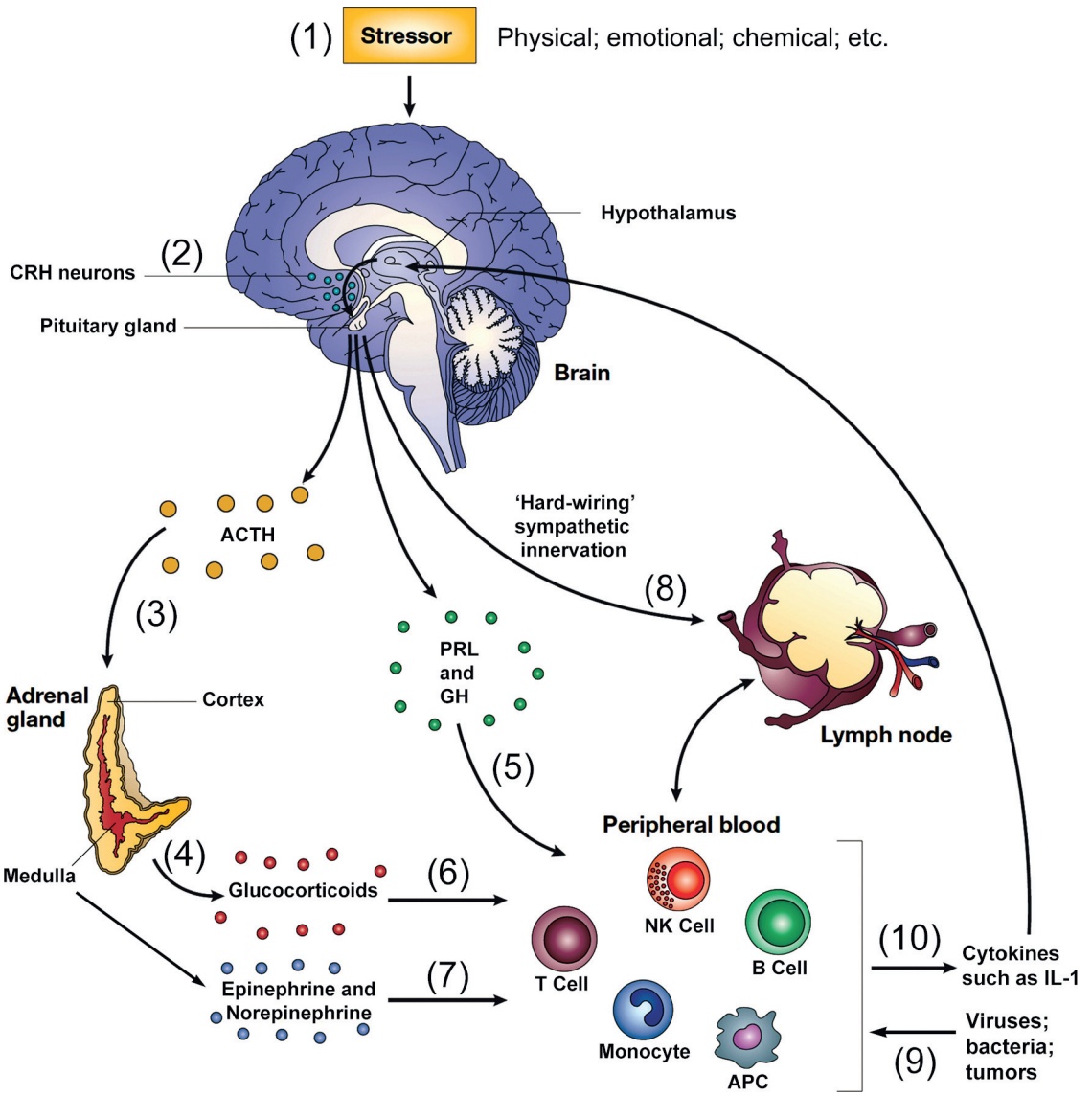

Figure 1.2 The body's three communication systems do not act independently

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

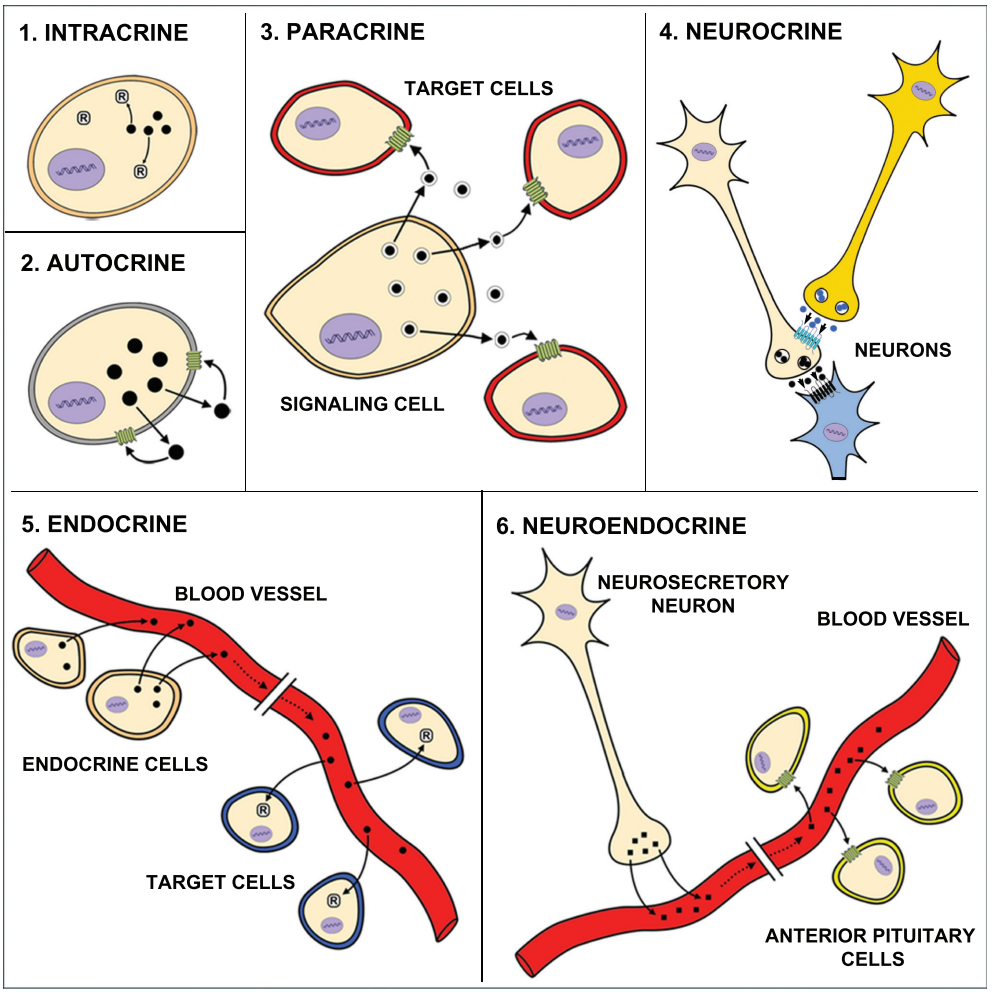

Figure 1.3 Methods of communication between cells of the (neuro)endocrine system
In *intracrine* communication (1) hormonal messengers, either synthesized in the same cell or imported from the bloodstream, act at intracellular receptors. In *autocrine* communication (2), hormones act on the cells that 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.

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