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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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)