Neurochemistry of Sleep and Wakefulness

Pharmacological approaches to our understanding of sleep have been at the forefront of sleep research for many years. Traditional techniques have included the use of pharmacological agonists and antagonists, as well as transmitter-specific lesions. These have been enhanced by the introduction of molecular genetics and the use of transgenes and targeted gene deletion. *Neurochemistry of Sleep and Wakefulness* is an exceptional, single source of information on the role of the major mammalian neurotransmitter systems involved in the regulation of sleep and waking. With contributions from internationally recognized experts, this book clearly describes how researchers have made use of the myriad techniques in their armamentarium to characterize the role of a given neurotransmitter in the regulation of sleep and waking. Suitable for experimental and clinical pharmacologists, the book will have wider appeal to sleep researchers, psychiatrists and any professional interested in the interdisciplinary areas of neurobiology and pharmacology.

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Neurochemistry of Sleep and Wakefulness

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To our wives, our families, our friends and our teachers,
Who have supported and helped us in all we have accomplished.
And, for one of us, to the memory of
My parents and a summer evening on the Via Appia Antica.

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Preface

Neurochemistry of Sleep and Wakefulness focuses on the actions and interactions of neurotransmitters involved in the control and modulation of the behavioral states that we know as waking and sleeping. It presents results and emerging concepts that in recent years have challenged our understanding about the basic brain systems that are involved in sleep and wakefulness. As might be expected, these new findings are also having an effect on the practice of sleep medicine. In fact, once considered a minor sub-specialty, sleep medicine is developing into a significant and growing area of medicine; and much of this growth can be attributed to improved knowledge about brain neurochemistry and the drugs that have been developed as a result.

Thus, inevitably, the relationship between sleep and the chemistry of neurotransmission has become an area of intense medical, biological, and scientific interest. It seemingly affects all facets of our health and well-being. But this relationship is also complex because it involves fundamental, yet still incompletely understood mechanisms and functions in the brain, most notably the essential difference between sleep and wakefulness. Although this field of research in its current form began with the identification of specific chemical neurotransmitter systems in the brain some forty years ago, we can actually date the beginning of research into sleep neurochemistry to the onset of the twentieth century. At that time sleep factors, or substances in cerebrospinal fluid or blood that build up during wakefulness and dissipate during sleep, were postulated and became the focus of research. Despite some initially promising results that seemed to support the idea, it eventually became evident that this hypothesis was conceptually far more complex than originally conceived. The history of this research is fascinating and is briefly summarized, together with the current consensus, in Chapter 11 of this volume.

Each chapter of *Neurochemistry of Sleep and Wakefulness* has been written by a knowledgeable expert or research team, each of whom is directly involved

in the investigations that they describe. This has ensured a text that is readily accessible to both basic and clinical sleep researchers, while covering the breadth of sleep neurochemistry in some detail. This volume thus brings together a collective scholarship in both basic and clinical research with interests that span neuroscience, neurochemistry, neuropharmacology, sleep pharmacology, and biological rhythms.

We have divided the volume into three parts. Part I comprises introductory chapters that summarize the neurochemistry and neurochemical mechanisms of specific states, including a review of the onset of sleep, and of rapid eye movement sleep and wakefulness. Then follows a group of chapters (Part II) that each focus on the relationship between sleep and a specific, well-characterized neurotransmitter system, such as acetylcholine and glutamate. Part III of the volume is devoted to more recent discoveries concerning neurochemical influences on sleep and wakefulness such as melatonin, the prostaglandins, and adenosine. Also in this part are included two chapters on neuropeptides, one of which, Chapter 14, reviews some interesting and potentially critical links between specific neuropeptides and sleep–wakefulness. The uniqueness of the findings described in this chapter is that the neuropeptides involved do not immediately relate to what is currently known about the neuroanatomical circuits of sleep and wakefulness. This suggests future research directions. The close interrelation between sleep and metabolism through hypothalamic neuropeptide circuits that were originally implicated in narcolepsy is underlined in Chapter 15. The volume concludes with a topical review, Chapter 16, which highlights the translation of neurochemical research into therapeutic development.

Neurochemistry of Sleep and Wakefulness is not exhaustive. For example, separate chapters could have been included for G-proteins and signaling cascades, glycine, uridine, lipid signaling, and neuroimaging. Knowledge is evolving rapidly in these areas, but they must await a future edition. However, the volume is current and will therefore be useful to sleep researchers, as well as to neuropharmacologists, neuroanatomists, neurophysiologists, and medical specialists. In addition, this book should prove valuable to medical students and clinicians who require an overall understanding of the field. We trust that the contents and organization of this volume will be both rewarding and interesting for our readers. Our hope is that it will encourage future advances in sleep research and these findings will eventually be themselves summarized in future editions.

As always, we welcome communication from our readers concerning the volume and its organization, and especially concerning any inaccuracies or omissions that remain. We take full responsibility for any such inaccuracies, and we would appreciate having them drawn to our attention.

Acknowledgements

Many individuals played instrumental roles in the conception, development, and completion of *Neurochemistry of Sleep and Wakefulness*. This enterprise was challenging, and the editors received help from many. We are delighted to acknowledge some of them here.

Firstly, we must thank our contributors. Without their involvement and dedication to the research they describe, this volume would not have been possible.

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Finally, we express our gratitude to our families for their patience and support. Thank you.

Abbreviations

3-MT	3-methoxytryptamine
5-HT	5-hydroxytryptamine (i.e. serotonin)
5-HTP	5-hydroxytryptophan
5-HIAA	5-hydroxyindoleacetic acid
7-NI	7-nitroindazole
8-PST	8-(p-sulfophenyl)-theophylline
ACh	acetylcholine
AChE	acetylcholinesterase
ACSF	artificial cerebrospinal fluid
ADA	adenosine deaminase
AFMK	*N*-acetyl-*N*-formyl-5-methoxykynuramine
AH	anterior hypothalamus
AHP	after hyperpolarization
AMP	adenosine monophosphate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid
ARC	arcuate nucleus
ATP	adenosine triphosphate
BF	basal forebrain
BH4	tetrahydrobiopterin
BZD	benzodiazepine
cAMP	cyclic adenosine monophosphate
cDNA	complementary deoxyribonucleic acid
CEA	central nucleus of the amygdala
cGMP	cyclic guanosine monophosphate
CHA	N6-cyclohexyladenosine
ChAT	choline acetyltransferase
ChT	choline transporter

CNS	central nervous system
CNT	concentrating nucleoside transporter
CoA	co-enzyme A
COX	cycloxygenase
CPA	N6-cyclopentyladenosine
CPDX	8-cyclopentyl-1,3-dimethylxanthine
CPT	cyclopentyltheophylline
CRE	cyclic-AMP response element
CREB	cyclic AMP response element binding protein
CRH	corticotrophin-releasing hormone
CSF	cerebrospinal fluid
CSN	cold-sensitive neuron
CST-14	cortistatin-14
CTb	cholera toxin B subunit
CYP	cytochrome P
DAG	diacylglycerol
DARPP	dopamine and cyclic adenoside 3′,5′-monophosphate
DAT	dopamine transporter
DBB	diagonal band of Broca
DL	dorsolateral
DMH	dorsomedial hypothalamic nucleus
DOMA	dihyroxymandelic acid
DOPAC	dihyroxyphenylacetic acid
DPGi	dorsal paragigantocellular reticular nucleus
DPMe	deep mesencephalic reticular nucleus
DR(N)	dorsal raphe (nucleus)
DSIP	delta-sleep-inducing peptide
DSPS	delayed sleep phase syndrome
ECS	electroconvulsive shock
EEG	electroencephalograph
EHNA	erythro-9-(2-hydroxy-3-nonyl)adenine
EMG	electromyogram
eNOS	endothelial nitric oxide synthase
ENT	equilibrative nucleoside transporter
EOG	electrooculogram
EPSP	excitatory postsynaptic potential
FDA	food and drug administration
GABA	γ-aminobutyric acid
GAD	glutamic acid decarboxylase
GHS-R	growth hormone secretagogue receptor

Glu	glutamate
Gly	glycine
GPi	globus pallidus, internal segment
GTP	guanosine triphosphate
HA	histamine
Hcrt	hypocretin
HDC	L-histidine decarboxylase
HIOMT	hydoxyindole *O*-methyltransferase
HLA	human leukocyte antigen
HNMT	histamine *N*-methyltransferase
HPLC	high-performance liquid chromatography
HVA	homovanillic acid
i.p.	intraperitoneal
i.c.v.	intracerebroventricular
IL-1	interleukin-1
IP3	inositol triphosphate
IPSP	inhibitory postsynaptic potential
IR	immunoreactivity
i.v.	intravenous
KO	knockout
L-DOPA	3,4-dihydroxy-L-phenylalanine (i.e. levodopa)
L-NAME	Nω-nitro-L-arginine methyl ester
L-PIA	N6(L-phenylisopropyl)adenosine
L-PGDS	leptomeningeal lipocalin-type prostaglandin D-synthase
LC	locus coeruleus
LD	light/dark
LDT	laterodorsal tegmentum
LH	lateral hypothalamus
LSD	lysergic acid diethylamide
LTS	low-threshold spike
mAChR	muscarnic cholinergic receptor
MAO	monoamine oxidase
MCH	melanin concentrating hormone
MDD	major depressive disorder
MEA	midbrain extrapyramidal area
mGlu(R)	metabotropic glutamate (receptor)
MHC	major histocompatibility complex
MnPN	median preoptic nucleus
mPOA	medial preoptic area
mPRF	medial pontine reticular formation

MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance image
MRN	median raphe nucleus
mRNA	messenger ribonucleic acid
MSLT	multiple sleep latency test
MT	melatonin
NA	noradrenaline
NADPH	nicotinamide adenine dinucleotide phosphate, reduced form
NAT	*N*-acetyltransferase
NE	norepinephrine
NECA	5′-*N*-ethylcarboxamide
NERT	norepinephrine reuptake transporter
NMDA	*N*-methyl-*D*-aspartate
NO	nitric oxide
NOS	nitric oxide synthase
NPS	neuropeptide S
NPY	neuropeptide Y
NREM	non-rapid eye movement
NRMc	nucleus reticularis magnocellularis
NRT	nicotine replacement therapy
NTS	nucleus of the solitary tract
OSA	obstructive sleep apnea
OX	orexin
PAG	periaqueductal gray
PCPA	p-chlorophenylalanine
PD	Parkinson's disease
PET	positron emission tomography
PF(L)H	perifornical (lateral) hypothalamus
PG	prostaglandin
PGO	ponto-geniculo-occipital
PH	posterior hypothalamus
PKA	protein kinase A
PKC	protein kinase C
PLC	phospholipase C
PLM	periodic leg movement
PnC	pontis caudalis
PNMT	phenylethanolamine *N*-methyltransferase
PnO	pontis oralis
PnOc	pontis oralis caudal

PnOr	pontis oralis rostral
POA	preoptic area
PP-1	protein phosphatase-1
PPT	pedunculopontine tegmentum
PRN	pontine reticular nucleus
PRO	pontis reticularis oralis
PS	paradoxical sleep
PTK	protein tyrosine kinase
PVN	paraventricular nucleus
PVT	thalamic paraventricular nucleus
RBD	REM sleep behavior disorder
REM	rapid eye movement
RHT	retinohypothalamic tract
RRF	retrorubral field
SCN	suprachiasmatic nucleus
SERT	serotonin reuptake transporter
SHA	*S*-adenosyl-homocysteine
SHMT	serine hydroxymethytransferase
SIN-1	3-morpholinosydnonimine
SN	substantia nigra
SNAP	*S*-nitroso-*N*-acetyl-1,1-penicillamine
SOREM	sleep onset REM
SPS	sleep promoting substance
SSRI	selective serotonin reuptake inhibitor
SWA	slow wave activity
SWS	slow wave sleep
t-MH	tele-methylhistamine
TCA	tricyclic antidepressant
TH	tyrosine hydroxylase
TMN	tuberomammillary nucleus
TNFα	tumor necrosis factor α
TrypH	tryptophan hydroxylase
TSD	total sleep deprivation
TTX	tetrodotoxin
TyH	tyrosine hydroxylase
UII	urotensin II
UV	ultraviolet
VAChaT	vesicular ACh transporter
VLPO	ventrolateral preoptic
VMAT	vesicular monoamine transporter

VTA	ventral tegmental area
WSN	warmth-sensitive neuron
WT	wild-type
α-FMH	α-fluoromethylhistidine
α-MHA	α-methylhistamine