Editor
S. R. Pandi-Perumal

Synopsis of SLEEP MEDICINE

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Edited by

S. R. Pandi-Perumal

APPLE ACADEMIC PRESS

Apple Academic Press Inc.
3333 Mistwell Crescent
Oakville, ON L6L 0A2
Canada

Apple Academic Press Inc.
9 Spinnaker Way
Waretown, NJ 08758
USA

Exclusive worldwide distribution by CRC Press, a member of Taylor & Francis Group

No claim to original U.S. Government works

Printed in the United States of America on acid-free paper

International Standard Book Number-13: 978-1-77188-346-7 (Hardcover)

International Standard Book Number-13: 978-1-77188-347-4 (eBook)

Library and Archives Canada Cataloguing in Publication

Synopsis of sleep medicine / edited by S.R. Pandi-Perumal.

Includes bibliographical references and index.
Issued in print and electronic formats.
ISBN 978-1-77188-346-7 (hardcover).--ISBN 978-1-77188-347-4 (pdf)

1. Sleep disorders. 2. Sleep disorders--Diagnosis. 3. Sleep disorders--Treatment.
4. Sleep--Physiological aspects. I. Pandi-Perumal, S. R., author, editor

RC547.S95 2016 616.8'498 C2016-904679-6 C2016-904680-X

Library of Congress Cataloging-in-Publication Data

Names: Pandi-Perumal, S. R., editor.
Title: Synopsis of sleep medicine / editor, S.R. Pandi-Perumal.
Description: Toronto ; New Jersey : Apple Academic Press, 2016. | Includes bibliographical references and index.
Identifiers: LCCN 2016030185 (print) | LCCN 2016031120 (ebook) | ISBN 9781771883467 (hardcover : alk. paper) | ISBN 9781771883474 (eBook) | ISBN 9781771883474 ()
Subjects: | MESH: Sleep Wake Disorders | Sleep Disorders, Circadian Rhythm
Classification: LCC RC547 (print) | LCC RC547 (ebook) | NLM WL 108 | DDC 616.8/498--dc23
LC record available at https://lccn.loc.gov/2016030185

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Dedication

To my family....

for their abundant support, for their patience and understanding, and for their everlasting love and affection.

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CONTENTS

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LIST OF ABBREVIATIONS

AANAT	Arylalkylamine N-acetyltransferase
AAP	American Academy of Pediatrics
AASM	American Academy of Sleep Medicine
AB	Awake bruxism
ABG	Arterial blood gases
AC	Alternate current
ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease
ADA	Americans with disabilities
ADCADN	Autosomal dominant cerebellar ataxia, deafness, and narcolepsy
ADHD	Attention deficit hyperactivity disorder
ADNOD	Autosomal dominant narcolepsy, obesity, and type 2 diabetes
AEs	Adverse experiences
AHI	Apnea–hypopnea index
AI	Apnea index
ALMA	Alternating leg muscle activation
AMP	Adenosine monophosphate-activated protein
AMPK	Adenosine monophosphate-activated protein kinase
AN	Autonomic nervous
APA	American Psychiatric Association
APAP	Auto-titrating positive airway pressure
APC	Antigen presenting cells
APPLES	Apnea positive pressure long-term efficacy study
AR	Allergic rhinitis
ArI	Arousal index
ASP	Advance sleep phase
ASPD	Advance sleep phase disorder
ASPS	Advanced sleep phase syndrome
ASV	Adaptive servo-ventilation
ASWPD	Advanced sleep-wake phase disorder
AVAPS	Average volume-assured pressure-support
Aβ	Amyloid-beta
BAC	Blood alcohol concentration
BAEP	Brainstem auditory evoked potentials
BMI	Body mass index
BPAP	Bi-level positive airway pressure
BSMI	Benign sleep myoclonus of infancy
BZD	Benzodiazepines
BZRAs	Benzodiazepine receptor agonists
C4-M1	Central-mastoid1
CAs	Confusional arousals
CBT	Cognitive behavioral therapy
CBT-I	Cognitive behavioral therapy for insomnia
CCGs	Clock-controlled genes
CD4+	Cluster of differentiation 4

CDC	Centers for Disease Control and Prevention
CH	Chloral hydrate
CKD	Chronic kidney disease
CKId	Casein kinase l delta
CKIe	Casein kinase I epsilon
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPS	Cycles per second
CPSC	Consumer product safety commission
CRH	Corticotropin-releasing hormone
CRSD	Circadian rhythm sleep disorder
CRSWD	Circadian rhythm sleep-wake disorders
Cry1	Cryptochrome 1
CSA	Central sleep apnea
CSAHS	Central sleep apnea-hypopnea syndrome
CSAS	Central sleep apnea syndromes
CSB	Cheyne-Stokes breathing
CSBS	Cheyne-Stokes breathing syndrome
CSF	Cerebrospinal fluid
CSF	Colony-stimulating factor
CSNK-I	Casein kinase-I
CSR	Cheyne-Stokes respiration
CT	Computed tomography
DA	Disorders of arousal
DA	Dopamine
DAT	Dopamine transporter
DC	Direct current
DEA	Drug Enforcement Agency
DEB	Dream-enactment behavior
DHEA	Dehydroepiandrosterone
DISE	Drug-induced sleep endoscopy
DLB	Dementia with Lewy bodies
DLMO	Dim light melatonin onset
DNA	Deoxyribonucleic acid
DORA	Dual orexin (hypocretin) receptor antagonist
DRN	Dorsal raphe nucleus
DSM-5	Diagnostic and statistical manual of mental disorders, 5th edition
DSPS	Delayed sleep phase syndrome
DSWPD	Delayed sleep-wake phase disorder
DZ	Dizygotic
ECG	Electrocardiography
ECG	Electrocardiogram
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
EEG	Electroencephalography
EFM	Excessive fragmentary myoclonus
EFNS	European Federation of Neurological Societies
EHS	Exploding head syndrome
EMA	European Medicines Agency
EMG	Electromyography
EMG	Electromyogram
EOG	Electrooculogram
EOG	Electrooculography
EPAP	Expiratory positive airway pressure
ESS	Epworth sleepiness scale
E_TCO_2	End-tidal CO2
F4-M1	Frontal4-Mastoid1

FDA	Food and Drug Administration
FFT	Fast Fourier transformation
fMRI	Functional MRI
FP	Follicular phase
FRC	Functional residual capacity
FSH	Follicle-stimulating hormone
GABA	Gamma-amino butyric acid
GAD	Generalized anxiety disorder
G-CSF	Granulocyte colony-stimulating factor
GDM	Gestational diabetes mellitus
GERD	Gastroesophageal reflux disorder
GH	Growth hormone
GHB	Gamma-hydroxybutyrate
GHRH	GH-releasing hormone
GHT	Geniculo-thalamic tract
GI	Gastrointestinal
GINA	Global initiative for asthma
GPCR	G protein-coupled receptors
gRLS	Gestational restless leg syndrome
H1N1	Hemagglutinin Type 1 and Neuraminidase Type 1
HAV	Hepatitis A vaccination
Hcrt	Hypocretin
HDL	High-density lipoprotein
HEENT	Head, eyes, ears, nose, and throat
HF	Heart failure
HFF	High frequency filter
HFT	Hypnagogic foot tremor
HIOMT	Hydroxyindole-O-methyltransferase
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPA	Hypothalamus-pituitary-adrenal
hPer2	Human Period2
HRQL	Health-related quality of life
HRT	Hormone replacement therapy
HTL	Hypothalamus
Hz	Hertz
ICAM	Intercellular adhesion molecule
ICD	International classification of diseases
ICSD	International classification of sleep disorders
ICSD-3	International classification of sleep disorders, 3rd edition
ICV	Intracerebroventricular
IDO	Indoleamine 2, 3-dioxygenase
IFN	Interferon
IH	Idiopathic hypersomnia
IL	Interleukin
IL-1β	Interleukin-1 beta
IPAP	Inspiratory positive airway pressure
IRT	Imagery rehearsal therapy
ISR	Intensive sleep retraining
ISWR	Irregular sleep-wake rhythm
ISWRD	Irregular sleep-wake rhythm disorder
IUGR	Intrauterine growth retardation
KLS	Kleine-Levin syndrome
LAEP	Late auditory evoked potentials
LAUP	Laser-assisted uvulopalatoplasty
LBW	Low birth weight

LC	Locus ceruleus
LC-AN	Locus ceruleus autonomic nervous
LD	Light-dark
LDL	Low-density lipoprotein
LDT-PPT	Laterodorsal and pedunculopontine tegmental nucleus
LFF	Low frequency filter
LGN	Lateral geniculate nucleus
LH	Luteinizing hormone
LM	Leg movement
LP	Luteal phase
LPS	Lipopolysaccharide
LSAT	Lowest oxygen desaturation indices
μV	Microvolt
MADs	Mandibular advancement devices
MAO-B	Monoamine oxidase type B
MAOIs	Monoamine oxidase inhibitors
MBSR	Mindfulness-based stress reduction
MCH	Melanin-concentrating hormone
MCI	Mild cognitive impairment
MCP-1	Monocyte chemoattractant protein-1
MEG	Magnetoencephalography
MES-amphetamine	Mixed salts/mixed enantiomers amphetamine
MHC	Major histocompatibility
MMA	Maxillomandibular advancement
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSA	Multiple-system atrophy
MSLT	Multiple sleep latency test
MT_1	Melatonin receptor1
MWT	Maintenance of wakefulness test
MZ	Monozygotic
NA	Nucleus of the amygdale
NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	Nicotinamide adenine dinucleotide phosphate
NASD	Non-apnea sleep disorders
NES	Night eating syndrome
NIH	National Institutes of Health
NK	Natural killer
NOS	Not otherwise specified
NREM	Non rapid eye movement
NSF	National Sleep Foundation
NTSB	National Transportation Safety Board
O2-M1	Occipital-mastoid1
OA	Oral appliances
OCD	Obsessive-compulsive disorder
OCST	Out-of-center sleep testing
ODI	Oxygen desaturation index
OHS	Obesity hypoventilation syndrome
OR	Odds ratio
OSA	Obstructive sleep apnea
OSAHS	Obstructive sleep apnea-hypopnea syndrome
OTC	Over-the-counter
$PaCO_2$	Pressure of carbon dioxide
PAP	Positive airway pressure
PAS	p-aminosalicylic acid
PCOS	Polycystic ovarian syndrome
PD	Parkinson's disease
PD	Panic disorder
PDR	Posterior dominant rhythm
PDSS	Parkinson's disease sleep scale

PET	Positron emission tomography
PFT	Pulmonary function tests
PGO	Ponto-geniculo-occipital
PHOX2B	Paired like homeobox 2b
PLM	Periodic leg movement
PLMD	Periodic limb movement disorder
PLMS	Periodic limb movements of sleep
PMDD	Premenstrual dysphoric disorder
PMR	Progressive muscle relaxation
POA	Preoptic area
POMC	Pro-opiomelanocortin
PPD	Post partum depression
PPN	Pedunculopontine nucleus
PS	Paradoxical sleep
PSG	Polysomnogram
PSG	Polysomnography
PSM	Propriospinal myoclonus at sleep onset
PSP	Progressive supranuclear palsy
PSQI	Pittsburgh sleep quality index
PTC	Pressor trigger of cataplexy
PTSD	Post-traumatic stress disorder
PTT	Pulse transit time
PVN	Paraventricular nucleus
QOL	Quality of life
RAAS	Reticular ascending activating system
RBD	REM sleep behavior disorder
RDI	Respiratory disturbance index
REM	Rapid eye movement
REMOL	REM onset latency
REMS	Risk evaluation and mitigation strategy
REMw/oA	REM sleep without atonia
RERAs	Respiratory effort-related arousals
RF	Reticular formation
RFA	Radiofrequency ablation
RHT	Retinohypothalamic tract
RIP	Respiratory inductance plethysmography
RISP	Recurrent isolated sleep paralysis
RLS	Restless legs syndrome
RMD	Sleep-related rhythmic disorder
RORA	Retinoic acid receptor related orphan receptor-A
RORα	Retinoic acid receptor related orphan receptor- alpha
RR	Risk ratio
RRE	Rev response element
RSWA	REM sleep without atonia
RWA	REM sleep without atonia
SA	Sleep attacks
SAD	Social anxiety disorder
SB	Sleep bruxism
SCN	Suprachiasmatic nucleus
SCT	Stimulus control therapy
SD	Sleep disturbances
SD	Standard deviation
SD	Sleep disordered breathing
S	Sleep efficiency
SEM	Slow eye movements
SGA	Small for gestational age
SHVS	Sleep hypoventilation syndrome
SIDS	Sudden infant death syndrome
SL	Sleep onset latency
SLD	Sub lateral dorsal nucleus

SN	Substantia nigra pars compacta
SNRIs	Selective noradrenergic reuptake inhibitors
SOREM	Sleep onset REM
SOREMP	Sleep onset REM period
SRED	Sleep-related eating disorder
SRMDs	Sleep-related movement disorders
SRT	Sleep restriction therapy
SSRIs	Selective serotonin reuptake inhibitors
STs	Sleep terrors
SUID	Sudden unexpected infant death syndrome
SW	Sleepwalking
SWD	Shift work disorder
SWS	Slow wave sleep
SXB	Sodium Oxybate
T cell	Thymocytes cell
TBI	Traumatic brain injury
TCAs	Tricyclic antidepressants
Th cells	Thelper cells
TMN	Tuberomammillary nucleus
TNF	Tumor necrosis factor
TRD	Tongue retaining devices
TSH	Thyroid-stimulating hormone
TST	Total sleep time
UARS	Upper airway resistance syndrome
UPPP	Uvulopalatopharyngoplasty
VCAM	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
VMS	Vasomotor symptoms
VTA	Ventral tegmental area
W	Wakefulness
WASO	Wake after sleep onset
WED	Willis-Ekbom disease

PREFACE

If anyone were to ask, "why did you decide to edit this volume?", one would immediately think of two answers: First, that they genuinely believed there is a need for a volume of this sort, and, second, that, however pretentious it might sound, they believed that, because of their years of teaching and research experience, he/she is the right person to edit it.

However, I have a third answer. I have, since the beginning of my scientific career, despite my background in botany, been involved in the sleep field. Having edited over 20 volumes along with leading experts in the field of sleep and biological rhythms, I believe that I now have the requisite experience to edit an introductory sleep medicine volume on my own. This first edition of this volume is aimed at residents, fellows, house officers, and physicians of various specialties as well as clinical sleep researchers. The volume will give a basic grounding in sleep medicine to those who are established in related specialties as well as to younger professionals who are considering a future career in sleep medicine. This volume attempts to convey something of the fascinating complexity of the field as well as to separate figure from ground for those who are newcomers to the field and who are seeking guideposts for further research. Sleep medicine encompasses an unusually board spectrum of contributions from biology, technology, and medicine. This volume seeks to summarize the considerable mass of knowledge that has now accumulated in the field and to impart its major findings in a manner that is both comprehensive but not overwhelming.

Inasmuch as sleep problems are frequently co-morbid with other medical conditions, the overt presenting symptoms of many patients may driven by a number of other factors. Disruptions to circadian organization may have a multiple effects of which sleep difficulties are simply the most visible. It is thus in the interest of clinicians to be alert to the ways in which sleep problems interconnect with other pathologies. It is often the case for instance that insomnia is not just insomnia, which is either a symptom or possibly a driver of correlated pathologies. It is thus in the interest of clinicians to be alert to this interconnectedness, and to recognize which difficulties are primary and which are not.

The literature on sleep and sleep medicine is enormous, and expanding rapidly. The objective of the editor has been to make this volume a useful tool for graduate students and newcomers who realistically do not always have time to check original publications. The authors have endeavored to give appropriate references to some of the more recent literature, and at the same time to quote the origins of some of the statements made.

There are often constraints to editing a volume, especially the first edition. For example, it is not always possible to address

all the topics that would be desirable for an introductory summary to cover. Additionally it is not always feasible to acquire the best experts in a special area. Nevertheless, for those who are interested in learning more about a specialized area of sleep medicine, the reference sections will represent a rich resource for this purpose. As with all major efforts of this kind we regard this introductory volume and those which will follow as "works in progress," and we anticipate that the content of future editions will evolve to respond to changes in the field as well as to the informational needs of our readers.

We have made every effort to ensure that the dosage recommendations are accurate and in agreement with the standards and collective opinion accepted at the time of publication. The formulations and usage described do not necessarily have specific approval by the regulatory authorities of all countries. Since dosage regimens may be modified as new clinical research accumulates, readers are strongly advised to make note of the most recently recommended prescribing guidelines in their respective countries. Every effort leading up to the creation of this volume has been to make it into a practical and useful introduction to the sleep medicine field. However, as editor I remain responsible for any errors or mistakes which have occurred. This first edition will, I hope, stimulate in you as much excitement and satisfaction as it has in us. I sincerely hope that this volume will serve as a comprehensive guide for diagnostic problems in sleep medicine and it will find its way into the places where the battle against sleep dysfunctions is waged daily in clinics and hospitals around the world.

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CREDITS AND ACKNOWLEDGEMENTS

I would like to thank some of the many people who have been instrumental in assisting me with the first edition of *Synopsis of Sleep Medicine*. First, I owe an enormous debt to Professor Colin M. Shapiro, Department of Psychiatry, University of Toronto, for getting me started in the field of sleep medicine. Early in my career he transformed me from being an agrostologist (the branch of botany concerned with grasses) to a sleep scientist. I have the deepest gratitude for his mentorship and friendship, and for the great privilege of receiving his contribution to this volume. This meant a lot to me. He is known for the inspiration that he has provided to all who have known him, including me.

At this juncture, I also would like to thank the mentorship of Prof. Martin R. Ralph, Prof. Mircea Steriade, Prof. Michael H. Chase, Prof. Rosalind Cartwright whose invitations to work with them to learn the field of sleep and biological rhythms and were the opportunities of a lifetime and helped to shape my career goals. Additionally, over the decades, I have collaborated with numerous individuals. It will be impossible to list every single one of them. A special mention goes to Prof. Jaime M. Monti, Prof. Daniel P. Cardinali, Prof. Gregory M. Brown, Prof. Ahmed S. BaHammam, Prof. Meera Narasimhan, Prof. Adam Moscovitch, and Mr. Warren Spence. If I am known in this field, they are the reason. All these individuals nurtured and mentored me in some way or other and helped me to become for what I am today.

I would like to thank Prof. Monica Levy Andersen, Department of Psychobiology, Universidade Federal de São Paulo, São Paulo, Brazil, who enthusiastically helped me in identifying some of the authors.

A special thanks to all those who invested time and effort in the compilation of the material that became this book. The many authors who contributed their expertise and perspectives are clearly the backbone of this project and they deserve the lion's share of the commendation. Over 55 biomedical professionals from industry and academia contributed to this work. Most certainly such a distinguished group of authors provided the needed balance and perspective.

I would like to particularly thank Mr. Ashish Kumar, President and Publisher of the Apple Academic Press, Canada, for the solicitation and encouragement in the development of this first edition. He has supported and guided this project from the beginning. I wish to acknowledge the professionalism of the editorial and production staff at the Apple Academic Press, who took on this new project and completed it with remarkable speed and flexibility.

On the top of everything else, I wish to acknowledge my family who provided the encouragement and support that make it possible. They are the reason for my accomplishments. All my books are, in the end, for them.

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NEUROANATOMY AND NEUROPHARMACOLOGY OF SLEEP AND WAKEFULNESS

Pablo Torterolo, Jaime M. Monti, and Seithikurippu R. Pandi-Perumal

ABSTRACT

Since the discovery of the ascending reticular activating system more than sixty years ago, the anatomy, electrophysiology, and neurochemistry of the neuronal networks involved in generating and maintaining wakefulness, that is, the activating systems have been characterized in detail. Furthermore, the neural areas critically involved in the generation and maintenance of rapid eye movement (REM) and non-REM (NREM) sleeps, which are called the hypnogenic systems, have also been delineated. The activating and hypnogenic systems deeply interact in order to induce the sleep/wakefulness cycle. These systems are modulated by the suprachiasmatic nucleus (SCN), the circadian rhythm pacemaker, as well as by various somnogenic substances such as adenosine and melatonin.

This chapter is a brief review on the neuroanatomy and functions of the activating and hypnogenic systems. The knowledge of neurobiological basis of these systems is crucial to understand the physiology of wakefulness and sleep, as well as to explain the pathophysiology of conditions such as insomnia, sleepiness, or abnormal behaviors during sleep (parasomnias). Additionally, the chapter highlights the concepts that can be easily applied to understand the neuropharmacology of sleep pathologies.

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1.1. INTRODUCTION

In humans, most mammals, and birds, three behavioral states can be readily distinguished: wakefulness (W), non-Rapid eye movement (NREM) sleep (also called slow wave sleep (SWS)), and rapid eye movement (REM) sleep. Polysomnography (PSG) is the basic tool used to differentiate these states. It consists of the simultaneous recording of various physiological parameters such as the electroencephalogram (EEG), the electromyogram (EMG), and eye movements; other bioelectrical signals can also be recorded in humans or experimental animals (Figure 1.1). The main features of the human PSG are summarized in Table 1.1.

During W, an optimal interaction with the environment allows the development of various behaviors necessary for survival. In humans, W is accompanied by awareness (consciousness) of the environment and internally generated stimuli such as hunger and thirst. The EEG recording of W is marked by the presence of high frequency and low amplitude (cortical activation, Figure 1.1) determined by the activity of thalamic and cortical neurons.

During sleep, there is a marked decrease in the interaction with the environment, an increase of the threshold for the reaction to external stimuli, and a decrease in somatomotor activity. Furthermore, animals adopt a distinctive position to conserve heat.

Presently, three NREM sleep phases (stages N1, N2, and N3 or SWS) are distinguished in humans according to the depth of the state. From stage W, normal adults enter in light NREM sleep (or stage N1). Stage N2 is characterized by the presence of sleep spindles and K-complexes, while the presence of low frequency (0.5–4 Hz) of high-amplitude delta waves characterizes the EEG during N3. Furthermore, tonic parasympathetic activity increases, determining characteristic changes in visceral activity. In the deeper stages of NREM sleep, cognitive activity (that is, dreams) is minimal (Dement and Kleitman, 1957; Pace-Schott, 2005).

REM sleep (or stage R) occurs periodically, and is always preceded by NREM sleep. REM sleep is a deep sleep stage although the EEG is similar to that of stage W; hence, it is also called "paradoxical" sleep. REM sleep is characterized by fast REMs that typically occupy 20–25% of total sleep in human adults. REM sleep occurs ~90 min after sleep onset. There are both *phasic* (episodic) and *tonic* (persistent) components in the stage R. Dreams occur mainly during REM sleep, which is also accompanied by muscle atonia as evidenced in the EMG channel (Figure 1.1), and phasic changes in autonomic activity. A shortened REM onset latency (REMOL; it is the interval between the sleep onset and the appearance of the first REM sleep episode) is a biological marker of primary depression. It is also considered to be a clinically significant pathological feature in other brain diseases.

In rats, a species commonly used in preclinical studies, W and sleep are defined by PSG as follows (Figure 1.1):

1) W, by the presence of low-voltage fast waves in frontal cortex, a mixed theta activity in occipital cortex, and relatively high EMG activity;
2) Light sleep, by the occurrence of high-voltage slow cortical waves

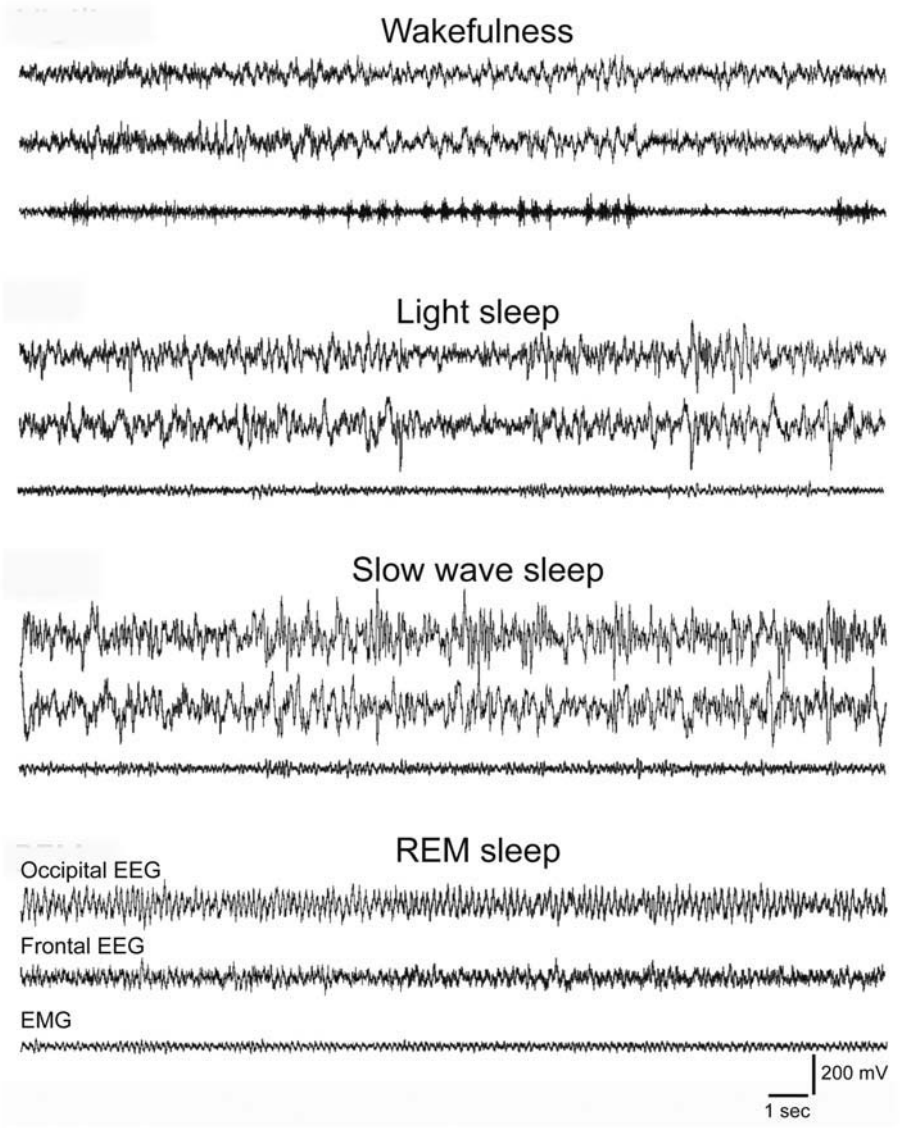

Figure 1.1: Polysomnographic recording during sleep and wakefulness in the rat. EEG, electroencephalogram; EMG, electromyogram.

Table 1.1: Electroencephalographic correlates of sleep stages.

		Characteristics			
Sleep stages	**TST (%)**	**EEG**	**EOG**	**EMG**	**Other variables**
Stage awake (relaxed wakefulness)		Alpha activity (8–12 Hz) or low-amplitude beta (13 35 Hz), mixed-frequency waves	REM (in sync or out of sync deflections), eye blinks	Relatively high tonic EMG activity	Alpha activity in occipital leads compared with central leads, eye opening suppresses alpha activity, movement artifacts
N1, formerly known as stage 1	2–5	Low-voltage, mixed-frequency waves (2–7 Hz range), mainly irregular theta activity, triangular vertex waves	SEMs, waxing and waning of alpha rhythm	Tonic EMG levels typically below range of relaxed wakefulness	Alpha ≤50%, vertex sharp waves in central leads, absence of spindles and K complexes
N2, formerly known as stage 2	45–55	Relatively low-voltage, mixed-frequency waves, some low-amplitude theta and delta activity	No eye movement	Low chin muscle activity	Sleep spindles (7–14 Hz) and K complexes occur intermittently
N3, formerly known as stages 3 and 4	5–20	≥20–50% of epoch consists of delta (0.5–2 Hz) activity	No eye movement	Chin muscle activity is lower than N1 and N2	Sleep spindles may be present
Stage REM	20–25	EEG is relatively low voltage with mixed frequency resembling N1 sleep	REM. Episodic rapid, jerky, and usually lateral eye movements in clusters	EMG tracing almost always reaches its lowest levels owing to muscle atonia	Phasic and tonic components, presence of sawtooth waves, alpha waves are 1–2 Hz slower than waves occurring during wakefulness and non-REM sleep

EEG, electroencephalography; EMG, electromyography; EOG, electrooculography; REM, rapid eye movement; SEMs, slow eye movements; TST, total sleep time.

interrupted by low voltage fast EEG activity;

3) SWS, by the occurrence of continuous high-amplitude slow frontal and occipital waves; light sleep + SWS is called NREM sleep;
4) REM sleep, by the presence of low-voltage fast frontal waves, a regular theta rhythm in the occipital cortex, and a silent EMG except for occasional myoclonic twitching.

Sleep in humans during the night shows four to five NREM-REM sleep cycles (the period from the sleep onset to the end of first REM episode or the period from the end of a REM sleep episode to the subsequent REM sleep episode). The average length of human sleep cycles is about 90–120 min. In contrast, the average sleep cycle duration of the rat is about 10 min (Trachsel et al., 1991).

1.2. COGNITIVE ACTIVITY THROUGH ACTIVATION OF THE THALAMUS AND THE CORTEX

Cognitive activities (consciousness and dreams) and the different EEG rhythms that support these functions are generated by the activity of cortical and thalamic neurons, which are mutually interconnected. Thalamic neurons have a complex electrophysiology that allows them to operate differently according to their level of polarization (Steriade et al., 1993). When hyperpolarized, the thalamic neurons that project to the cortex (thalamocortical neurons) oscillate at low frequency (0.5–4 Hz, delta rhythm), and tend to block the information toward the cortex that goes through the sensory pathways. This "oscillatory mode" of function synchronizes the cortical neurons and accompanied by other phenomena, generates the slow waves of NREM sleep. On the contrary, when these neurons are relatively depolarized, they enter in the "tonic mode" of function. In this condition, the thalamocortical neurons transmit sensory information toward the cortex in a reliable way. This mode of function occurs during W and REM sleep.

Therefore, the thalamus is critical for the generation of slow waves and spindles that characterize NREM sleep. When the thalamus is lesioned as it occurs in the "fatal familial insomnia," the generation of these electrographic signs is blocked and sleep is prevented (Montagna, 2005).

Neurons that form part of the activating system, that is, the neuronal system that generates and maintains wakefulness are summarized in Figure 1.2. The activating neurons project directly to the thalamus and/or the cortex (Jones, 2005). They depolarize thalamic neurons in order to produce the thalamic tonic mode and desynchronization (activation) of the EEG that accompanies the behavioral awakening. Part of the activating system (the cholinergic nuclei) is also active during REM sleep and activates the corticothalamic system during this behavioral state.

1.3. THE ACTIVATING SYSTEM

Which are the neural mechanisms involved in the generation and maintenance of the behavioral states?

In the 1930s, before REM sleep discovery, Bremer proposed that the baseline state of the brain was sleep (Bremer, 1935). His proposal was based on experimental transections at the level of the intercollicular region of the midbrain, in a prepa-

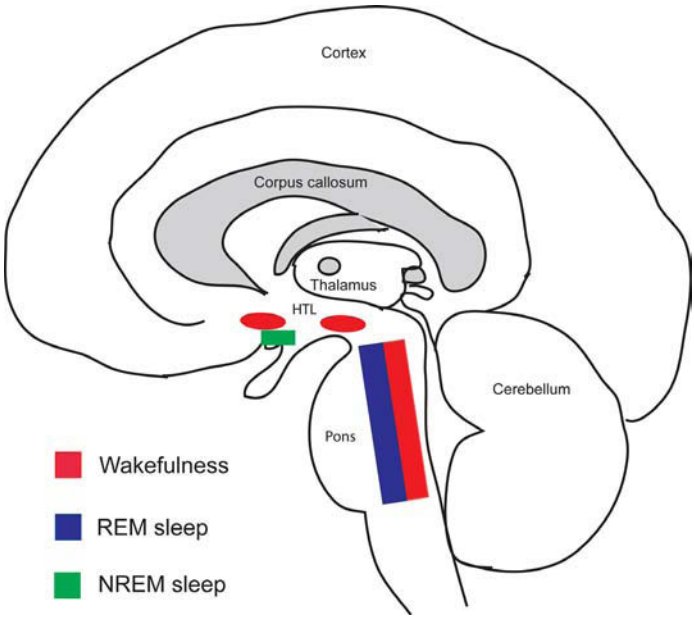

Figure 1.2: Activating (labeled in red) and hypnogenic (labeled in blue for REM sleep and green for NREM sleep) systems are shown. HTL, hypothalamus.

ration known as "cerveau isolé" ("isolated forebrain"). Animals with this injury had an EEG similar to that observed during NREM sleep. Since these animals had lesions in the ascending sensory pathways at the level of the midbrain, at that time it was considered that sleep occurred because sensory inputs to the diencephalon and telencephalon were reduced. In other words, sensory activity was viewed as necessary to maintain W. It was considered that the sensory blockade accompanied by ill-defined neuronal "fatigue," was the cause of sleep. This concept was known as the passive hypothesis of sleep (or deafferentation).

In 1949, Moruzzi and Magoun published their seminal work entitled: *Brainstem reticular formation and activation of the EEG* (Moruzzi and Magoun, 1949). This work is considered one of the most influential contributions in the field, and it inspired numerous investigations in the following decades. The reticular formation (RF) is located in the central area of the brainstem. Neurons in this region are not grouped in nuclei but are arranged in a complex mesh or network. This region is characterized by its high connectivity, receiving afferents from different sources and sending efferents to different sectors of the central nervous system (CNS) (Jones, 1995). Moruzzi and Magoun (1949) performed electrical stimulation at different rostrocaudal levels of the RF. Their main finding was that electrical stimulation of the RF activates the EEG during anesthesia, that is, from an EEG with high-amplitude and low-frequency waves (SWS-

like), the stimuli induced a high frequency, low amplitude EEG as in W. The activation of the EEG was widespread (throughout the neocortex) and in lightly anesthetized animals, it was accompanied by behavioral awakening.

The role of the midbrain and pontine RF in generating and maintaining W was confirmed later making use of different approaches. This area along with its ascending projection was called "reticular ascending activating system" (RAAS). Of note, lesions of this area in patients and experimental animals generate a coma condition (Lindsley et al., 1950; Plum and Posner, 2000).

At the time of its discovery, the RAAS did not contradict the "passive" hypothesis of sleep, but complemented it. It was believed that sleep is initiated by the progressive inactivation of the RAAS, where the decrease in sensory input played a major role. This hypothesis was named "passive inactivation of the RF" or "reticular sleep hypothesis."

The activation of the RAAS promotes the thalamocortical activation (as evidenced by EEG desynchronization) that supports cognitive awakening. The arousal reaction is accompanied by motor, autonomic, and endocrine changes. Then, the RF would also modify directly or indirectly, the activity of motoneurons, autonomic preganglionic neurons, and hypothalamic endocrine-related neurons. In this review, we will emphasize aspects related to the cognitive awakening and EEG activation. Therefore, only the upward or ascending (thalamocortical) component of the RAAS will be considered.

The identification of specific neuronal groups that use different neurotransmitters was the beginning of a new era for understanding the RF and the RAAS. Furthermore, different experimental approaches allowed obtaining details of the physiology of the activating system. Nowadays, the following concepts have been established: (i) The RAAS is composed of various neuronal groups that differ in their neurotransmitters; (ii) the neurons from specific regions of the posterior and lateral (perifornical) hypothalamus and basal forebrain, that are considered the rostral extension of the RF of the brainstem, behave as activating nuclei. Thus, the RAAS, the posterior and posterolateral hypothalamus, and the basal forebrain constitute the activating system; (iii) the neuronal groups that make up the activating systems project through a dorsal pathway toward the specific and non-specific thalamic nuclei, and/or a ventral pathway passing through the lateral hypothalamus, and basal forebrain toward the cerebral cortex.

The different components of the activating system are discussed below.

1.3.1. Mesopontine Glutamatergic Neurons

Anatomical and functional studies have shown that the main component of the RAAS is located within the mesopontine RF. With respect to the glutamatergic neurons, they do not form a specific group but are distributed throughout the mesopontine RF intermingled with specific neuronal groups. Regarding their functional activity during the sleep–wakefulness cycle, mesopontine W/REM-on, REM-on, or W-on glutamatergic neurons have been identified (Boucetta et al., 2014).

It has been contended that ketamine, a *N-methyl-D-aspartate* (NMDA) glutama-

tergic antagonist, inhibits W and produces sedation, hypnosis, or pharmacological coma; part of these effects could be produced by reducing the synaptic effects of mesopontine glutamatergic neurons (Wolff and Winstock, 2006).

1.3.2. Noradrenergic Neurons of the Locus Coeruleus

The locus coeruleus (LC) is a noradrenergic nucleus located in the mesopontine dorsolateral region. The ascending projections of this nucleus are part of the dorsal pathway to the thalamus, and are also included in the ventral pathway that project directly to the cerebral cortex. LC noradrenergic neurons show their maximum firing rate during W; it decreases during NREM sleep and is minimal during REM sleep (Aston-Jones and Bloom, 1981). This profile of activity is in agreement with the pattern of release of noradrenaline in the cerebral cortex as measured by microdialysis (Berridge and Abercrombie, 1999). It should be mentioned that during W, these neurons markedly increase their firing rate following a new stimulus, but the response is reduced after habituation, which led to the proposal that this neuronal group regulates attention (Foote et al., 1991). Interestingly, a1 antagonists including prazosin facilitate the generation of sleep, while a2 agonists such as dexmedetomidine inhibit the activity of LC neurons and are used as sedatives (Nishino and Mignot, 1997; Nelson et al., 2003).

1.3.3. Midbrain Dopaminergic Neurons

The substantia nigra pars compacta (SN) and the ventral tegmental area (VTA) are located in the midbrain. Both regions are characterized by the presence of dopaminergic neurons; while dopaminergic neurons of the SN project to the dorsal striatum, VTA neurons project to the prefrontal cortex and nucleus accumbens (ventral striatum) (Oades and Halliday, 1987). The firing rate of dopaminergic neurons and extracellular concentration of dopamine in the prefrontal cortex increases during reward-related stimuli (Mirenowicz and Schultz, 1996; Feenstra, 2000). Dopamine agonists and antagonists increase and decrease W, respectively (Monti and Monti, 2007; Monti and Jantos, 2008). Presently available evidence tends to indicate that these dopaminergic neurons are involved in the arousal that accompanies reward and motivation. Cocaine and amphetamines inhibit dopamine reuptake and induce its release, respectively. As expected, their administration produces an increase of W. In addition, these drugs are strong positive reinforcers, which is because of their addictive power. Notwithstanding this, drugs that increase synaptic dopamine levels are in the first-line for the treatment of hypersomnia (Nishino and Mignot, 1997).

1.3.4. Serotonergic Neurons of the Rostral Raphe Nuclei

Serotonergic neurons of the dorsal (Figure 1.3A) and median raphe nuclei are located within the mesopontine midline (Jacobs and Azmitia, 1992; Monti, 2010b, a). These neurons project toward the thalamus and cortex. Serotonergic neurons discharge more frequently during W, decrease their activity during NREM sleep, and virtually turn off during REM sleep (McGinty and Harper, 1976). A similar pattern of

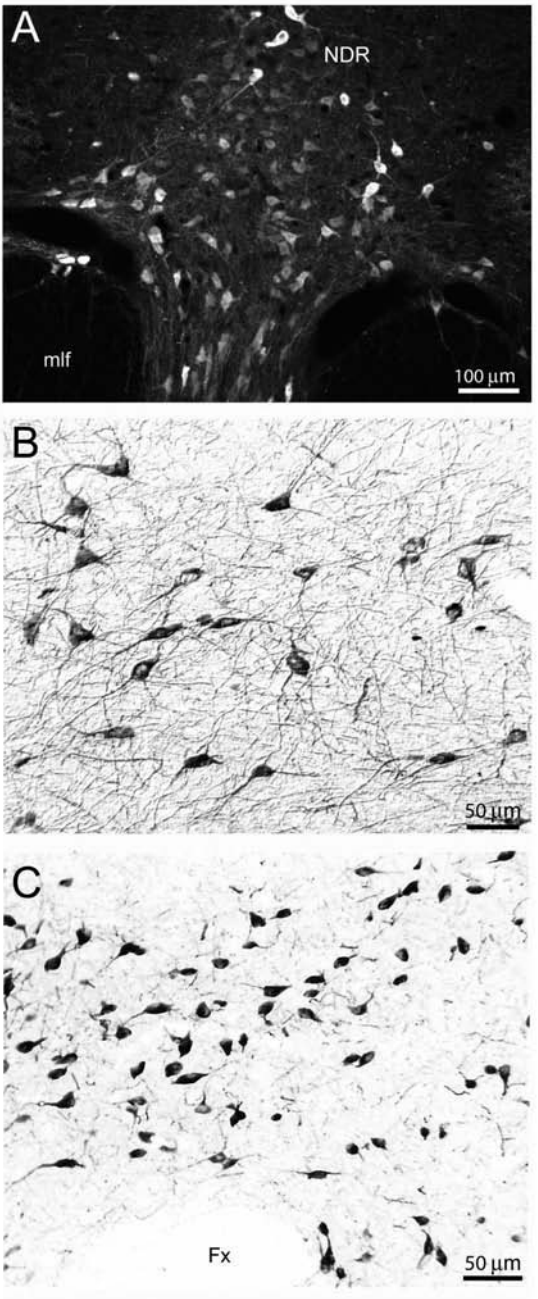

Figure 1.3. (A) Photomicrographs illustrating serotonergic neurons of the dorsal raphe nucleus of the rat; (B) cholinergic neurons of basal forebrain of the cat, and; (C) hypocretinergic neurons of the guinea pig. These neurons were revealed following immunohistochemistry procedures.

activity has been observed with respect to the release of serotonin as measured by microdialysis (Portas et al., 2000). Subgroups of these serotonergic neurons are activated during stereotyped movements that take place when the experimental animal is moving or grooming (Jacobs and Fornal, 2008). In turn, electrical stimulation of the dorsal raphe nucleus produces a marked EEG activation (Dringenberg and Vanderwolf, 1997). It has been proposed that serotonergic neurons play a permissive role in the generation of REM sleep such that they must be inhibited for REM sleep to occur (McCarley, 2007). Local GABAergic neurons would be involved in this inhibition (Torterolo et al., 2000). Since there are several types of receptors for serotonin, the effect of serotonergic drugs on sleep is complex (Monti and Jantos, 2008).

1.3.5. Cholinergic Neurons of the LDT-PPT

Mesopontine cholinergic neurons are located in the laterodorsal and pedunculopontine tegmental nucleus (LDT-PPT). These neurons project directly to the thalamus (Satoh and Fibiger, 1986). Cholinergic neurons are activated during W in close relation to the cortical activation. They are inhibited during NREM sleep and re-activated during REM sleep (Boucetta et al., 2014). In the thalamus, acetylcholine acts on muscarinic and nicotinic receptors in order to produce cortical activation (Curro Dossi et al., 1991). In humans, increasing synaptic levels of acetylcholine by acetylcholinesterase inhibitors produces W and cortical activation, while REM sleep precipitates if this drug is applied during NREM sleep (Gillin and Sitaram, 1984). These data suggest a bimodal role of cholinergic neurons, promoting both the generation of W and REM sleep. Of note, drugs that increase synaptic levels of acetylcholine, such as physostigmine, reverse the state of general anesthesia produced by *sevoflurane* in humans (Plourde et al., 2003).

1.3.6. Mesopontine GABAergic Neurons

GABAergic neurons, terminals, and receptors are distributed throughout the mesopontine region. In contrast to the effects of hypnotics that enhance GABAergic neurotransmission and facilitate sleep, the application of GABAergic receptor agonists into the NPO generates W (Xi et al., 1999). Furthermore, local increase of GABA levels in the NPO prolongs the time necessary to induce general anesthesia, while isoflurane anesthesia reduces GABA levels within the NPO (Vanini et al., 2008).

1.3.7. Histaminergic Neurons of the Posterior Hypothalamus

Neurons using histamine as a neurotransmitter are located only in the tuberomammillary nucleus of the posterior hypothalamus, and project to the thalamus and cortex (Monti, 2011). The firing rate of the histaminergic neurons decreases when passing from W to NREM sleep and is minimal during REM sleep (Takahashi et al., 2006).

The information provided by "knockout" mice lacking histidine decarboxylase (enzyme involved in the synthesis of histamine) is revealing; these animals are unable to stay awake when they are placed in a new environment (Parmentier et al., 2002). Drugs that increase synaptic levels of

histamine augment cortical activation and W (Kalivas, 1982). In humans, drugs that antagonize the H1 receptor including pyrilamine and diphenhydramine and have been prescribed as anti-allergic, cause drowsiness as a side effect (Roth et al., 1987).

1.3.8. Hypocretinergic Neurons of the Posterior Hypothalamus

In 1998, two independent research groups identified hypocretins almost simultaneously by different techniques (de Lecea et al., 1998; Sakurai et al., 1998). Hypocretin 1 and 2 (also called orexin A and B) neuropeptides are synthesized by a small group of neurons located exclusively in the dorsal, posterior, and lateral hypothalamic region (de Lecea et al., 1998; Sakurai et al., 1998) (Figure 1.3C). These neurons use the hypocretins as neurotransmitters and project diffusely throughout the CNS, including mesopontine areas critical for waking and sleep generation (Figure 1.4). Hypocretins act on two types of metabotropic receptors exerting presynaptic and postsynaptic excitatory effects.

The intracerebral or intraventricular administration of hypocretins facilitates the generation of W (Piper et al., 2000). In turn, several experimental approaches have shown that these neurons are primarily activated during motivated W; their activity is reduced during NREM sleep and is almost absent during tonic REM sleep; however, hypocretinergic neuronal activity seems to increase in the presence of the phasic components of REM sleep.

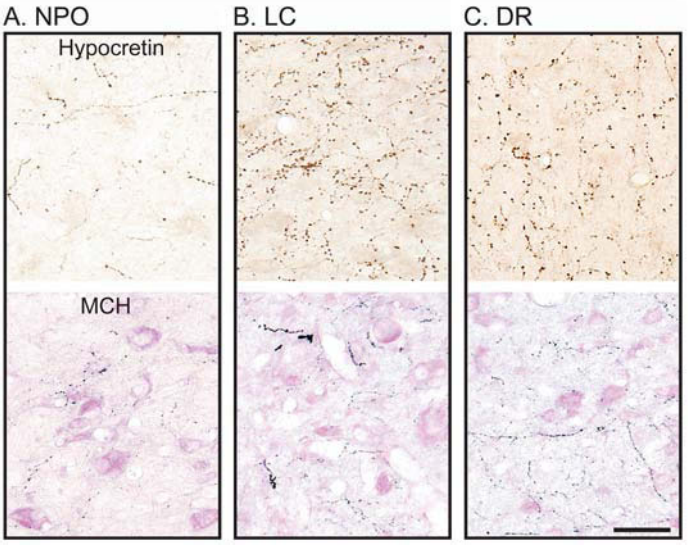

Figure 1.4. Hypocretinergic (above) and MCHergic (below) fibers in the nucleus pontis oralis (A. NPO), locus coeruleus (B, LC), and dorsal raphe nucleus (C, DR) of the cat. The sections were prepared for immunohistochemistry to detect hypocretin-1 and MCH. The sections treated with MCH antibodies (below) were also counterstained with pyronin-y. Calibration bar, 100 mm. This figure highlights the strong interconnection among the neurons that are critically involved in the generation of sleep and wakefulness.

(Torterolo et al., 2001b; Kiyashchenko et al., 2002; Torterolo et al., 2003; Lee et al., 2005b; Mileykovskiy et al., 2005; Torterolo et al., 2009c; Torterolo and Chase, 2014). The medical importance of this system boosted when Nishino et al., (2000) showed the absence of hypocretin 1 in the cerebrospinal fluid of narcoleptic patients; degeneration of these neurons is the pathological basis of narcolepsy-cataplexy.

1.3.9. Basal Forebrain Cholinergic Neurons

These cholinergic neurons are located in the area known as basal forebrain (anterior to the hypothalamus), which includes the nucleus basalis of Meynert (Figure 1.3B). The main projections of these neurons are to the neocortex, hippocampus, and reticular thalamic nucleus (Semba, 2000). Chemical and electrical stimulation of this region generates cortical activation and W, whereas its inactivation produces NREM sleep (Belardetti et al., 1977; Cape and Jones, 2000). During W and REMS, there is an increase in the firing rate of basal forebrain cholinergic neurons which is correlated with EEG activation and an increase in the release of the acetylcholine at cortical levels (Marrosu et al., 1995; Lee et al., 2005a). During W, these neurons regulate sensory information processing, attention, and learning. Of note, cognitive disorders characteristic of Alzheimer's disease are related to lesions of this neuronal group (Coyle et al., 1983; Vitiello and Borson, 2001).

1.3.10. Role of Wake-Promoting Neurons in the Different Types of Wakefulness

There is an important anatomical and functional relationship between the activating neuronal groups (Figure 1.4), which tends to indicate that these neurons act in tandem to generate and maintain W. W is a heterogeneous process. Thus, it is not the same as state of W when caused by nociceptive stimulation, by intense motor activity, or just during relaxed activity. There is evidence showing that the relative activity of the different components of the activating system varies with the type or level of W. For example, experimental studies using Fos protein as an index of neuronal activity have shown that the hypocretinergic neuronal activity increases during W with motor activity related to the motivation to explore a new environment, but not during quiet wakefulness or forced locomotion (Figure 1.5) (Torterolo et al., 2001b; Torterolo et al., 2003; Torterolo et al., 2009c). Moreover, serotonergic neurons are active during W related to stereotyped and automatic motor activity, while LC noradrenergic neurons would be critical in the increased surveillance that occurs following a new stimulus (Foote et al., 1991; Jacobs and Fornal, 2008).

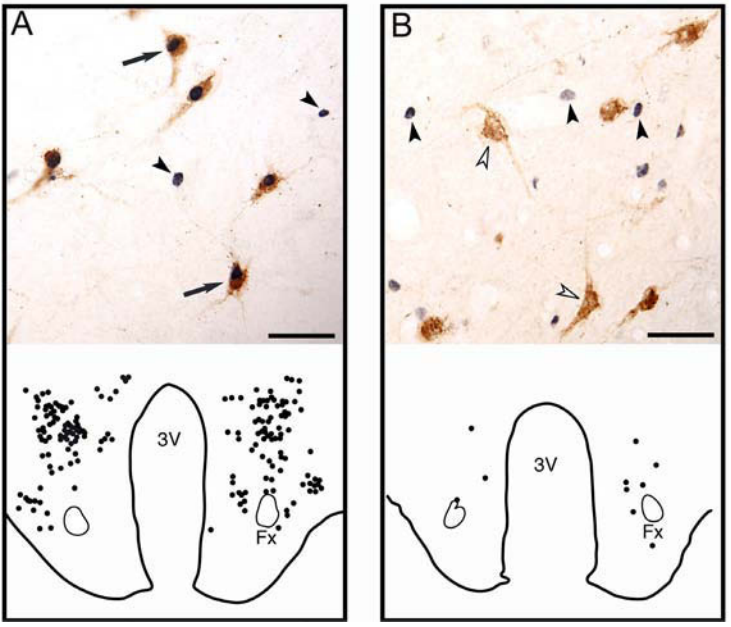

Figure 1.5. Photomicrographs illustrating hypocretin and Fos (a marker of neuronal activity) immunoreactive neurons from the posterolateral area of the hypothalamus. (A) Above, hypocretinergic neurons that express c-Fos (arrows) during active wakefulness with motor exploratory activity. Hypocretinergic neurons are stained in brown, Fos immunoreactivity, which is black, is restricted to nuclei. Hcrt- Fos+ neurons (arrowheads) are also intermingled with Hcrt+ Fos+ neurons. Below, camera lucida drawing of a representative hypothalamic sections of the same animal. The distribution of Hcrt+ Fos+ neurons is represented. Each mark indicates one labeled neuron (3V, third ventricle; Fx, fornix). (B) Above, group of hypocretinergic neurons during quiet wakefulness. The hypocretinergic neurons shown did not express c-Fos (unfilled arrowheads, i.e., not active), although Hcrt- Fos+ neurons are intermingled with these neurons (filled arrowheads). Below, the distribution of Hcrt+ Fos+ neurons in a representative section for the same animal is shown. This figure highlights the fact that hypocretinergic neurons are active during active wakefulness, but not during quiet (relaxed) wakefulness. Modified from Torterolo et al. (2001b).

1.4. HYPNOGENIC SYSTEMS

1.4.1. NREM Sleep: Preoptic Area

The neuronal groups critical in the generation and maintenance of NREM sleep are located in the preoptic area (POA) of the hypothalamus (Kumar, 2004; Szymusiak et al., 2007; Torterolo et al., 2009a; Benedetto et al., 2012) (Figure 1.2). These neurons, increase their firing rate during NREM sleep, and have been identified in the medial, median, and ventrolateral region of the POA. Electrical stimulation of the POA and adjacent basal forebrain induces NREM sleep and inhibits the activating system; in fact, GABAergic neurons of the POA project toward the activating system (McGinty and Szymusiak, 2005).

In turn, neurons from the activating system inhibit hypnogenic regions (Gallopin et al., 2000). This reciprocal inhibition between activating and hypnogenic neurons is critical for the transition between sleep and W.

1.4.2. REM Sleep Generation

The necessary and sufficient neuronal networks critical for the generation and maintenance of REM sleep are located in the mesopontine RF, where the RAAS is located (Figure 1.2) (Siegel, 2011). In fact, the LC noradrenergic neurons, and the dorsal raphe nucleus serotonergic neuron are active during W but turn off their firing during REM sleep (REM off neurons). Conversly, cholinergic neurons of the LDT-PPT increase their firing rate during REM sleep, thus contributing to the cortical activation of this state (McCarley, 2007; Boucetta et al., 2014). These cholinergic neurons also project to the NPO that is the executive area for REM sleep generation. Then, acetylcholine is released within this area to induce REM sleep. This effect is mimicked by microinjection of carbachol, a mixed (nicotinic and muscarinic) cholinergic agonist, into the NPO of a cat. Carbachol generates a long duration (up to 2 h) REM sleep episode with a very short latency (down to 30 s) (Figure 1.6). Physiologically, it is considered that cholinergic neurons of the LDT-PPT activate glutamatergic neurons of the NPO. In turn, these neurons activate different groups of neurons that execute REM sleep functions such as atonia, REMs, EEG activation, autonomic unsteadiness, and so forth. For example, REM sleep atonia depends upon glutamatergic neurons of the NPO that project to the magnocellular medullary RF and depolarize premotor glycinergic neurons (Chase, 2013). These neurons produce the postsynaptic inhibition of motoneurons during REM sleep.

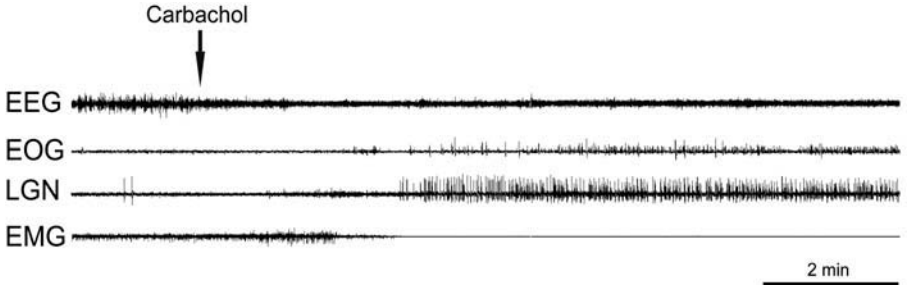

Figure 1.6. Polygraphic recording during the onset of an episode of REM sleep induced by a microinjection of carbachol into the nucleus pontis oralis of the cat. REM sleep is signaled by the appearance of ponto-geniculo-occipital (PGO) waves in the lateral geniculate nucleus (LGN), a decrease in muscle tone, REMs, and EEG desynchronization. This episode of REM sleep was maintained for approximately 2 h. An arrow signals the beginning of the microinjection of carbachol into the nucleus pontis oralis. EEG, electroencephalogram; EOG, electrooculogram; EMG, electromyogram; NGL, electrogram of the lateral geniculate nucleus (visual thalamus).

GABAergic neurons of the mesopontine area (dorsal raphe nucleus, LDT-PPT, ventrolateral periaqueductal gray, and so forth) also play an important role in the generation of REM sleep (Torterolo et al., 2000, 2001a; Torterolo et al., 2002a; Torterolo et al., 2002b; Vanini et al., 2007; Torterolo and Vanini, 2010). In fact, there are models which propose that REM sleep generation depends upon the activity of mesopontine GABAergic neurons (Lu et al., 2006; Luppi et al., 2007).

The hypothalamus also participates in the generation of REM sleep. As mentioned before, histaminergic neurons are REM-off. Moreover, hypocretinergic neurons decrease their firing rate during "tonic" REM sleep; however, Fos protein and microdialysis studies conducted in cats suggest that these neurons may be active during the "phasic" components of REM sleep, and may contribute to the induction of twitches, REMs, autonomic instability, and so forth (Torterolo and Chase, 2014). The role of the hypothalamic melanin-concentrating hormone (MCH) will be described in the next section.

1.4.3. Melanin-Concentrating Hormone: A Sleep Promoting Factor

There are neurons in the posterolateral hypothalamus (intermingled with the hypocretinergic neurons) and incertohypothalamic area that utilize the neuropeptide MCH as a neuromodulator (Torterolo et al., 2006; Torterolo et al., 2011a; Monti et al., 2013), and project throughout the CNS, including the mesopontine RF, where the RAAS is located (Figure 1.4) (Bittencourt et al., 1992). These neurons fire scarcely during W, increase their firing rate during NREM sleep, and reach a maximum during REM sleep. Since, the administration of MCH into the cerebral ventricles, preoptic area, basal forebrain, dorsal raphe nucleus, LC, and NPO facilitates the generation of NREM sleep and/or REM sleep, it is possible that MCHergic neurons inhibit the activating systems and/or activate the hypnogenic nucleus in order to promote sleep (Verret et al., 2003; Lagos et al., 2009; Torterolo et al., 2009b; Lagos et al., 2012; Benedetto et al., 2013; Monti et al., 2015a). Recent studies have demonstrated that MCH inhibits dorsal raphe nucleus serotonergic neurons (Devera et al., 2015); this finding may explain, at least in part, the promotion of REM sleep induced by MCH (Lagos et al., 2009). The suppression of the serotonergic activity by MCH could explain also the pro-depressive effect of this neuropeptide (Lagos et al., 2011; Lopez Hill et al., 2013; Urbanavicius et al., 2014).

1.5. TRANSITION FROM WAKEFULNESS TO NREM SLEEP

The physiological transition between W and sleep is regulated by a circadian and a homeostatic component (Borbely, 1982). Like all circadian rhythms, sleep and W are regulated by commands from the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN receives photic information directly from the retina, and regulates the activity of both the hypnogenic and activating systems (Mistlberger, 2005). Furthermore, through indirect modulation of the sympathetic system, the SCN regulates the release of melatonin from the pineal gland during the night (Pandi-Perumal et

al., 2008). Melatonin has a weak sleep-promoting effect.

The homeostatic component also regulates the sleep–wakefulness cycle, that is, prolonged W facilitates the generation of sleep. Different lines of research have shown that sleep-promoting substances including adenosine, are released and accumulated during W (Basheer et al., 2004; Huang et al., 2011). Adenosine promotes sleep by inhibiting the activating systems and stimulating the hypnogenic systems. Of interest, caffeine promotes W by blocking the receptors for adenosine (Nishino and Mignot, 2005).

1.6. TRANSITION FROM NREM SLEEP TO REM SLEEP

There is limited knowledge about the neuronal basis involved in the transition from NREM sleep to REM sleep. However, a role for the caudolateral peribrachial region during this transition has been proposed (Torterolo et al., 2011b).

1.7. BRIEF SYNOPSIS OF THE NEUROPHARMACOLOGY IN SLEEP PATHOLOGY

Knowing the neurobiological basis of W and sleep provides the clinician with the frame to understand sleep pathologies and the pharmacological approaches to their treatment.

Sleep pathological conditions are characterized by either a lack of the necessary amount (or quality) of sleep that is called insomnia, or by an excess of sleep, that is hypersomnia. Another type of syndromes is caused by the appearance of abnormal behaviors during sleep and is called parasomnias.

The chronic insomnia disorder in adult patients occurs no less than three times per week, for at least three months and is characterized by an inability to fall or stay asleep, and daytime complaints such as somnolence and fatigue (American Academy of Sleep Medicine, 2005). Medications approved for this disorder include benzodiazepine (BZD) receptor allosteric modulators, BZD (triazolam, temazepam, and flurazepam) or non-BZD (zolpidem, eszopiclone, and zaleplon) agents. These drugs promote sleep, at least in part, by reducing the activity of the activating systems. Melatonin and the melatonin receptor agonist ramelteon are also used for the treatment of an insomnia disorder; these drugs make the most of the sleep-promoting effect of natural melatonin. Low-dose doxepin (a tricyclic antidepressant) is also employed for the treatment of sleep disorders. Its mechanism of action is mainly related to the blockade of histamine H1 receptor. Finally, the dual orexin (hypocretin) receptor antagonist (DORA) suvorexant that blocks the effect of endogenous hypocretin (a wake-promoting neuromodulator), has been recently approved by the FDA for the treatment of insomnia disorders.

Briefly, drugs currently used for the treatment of chronic primary insomnia address sleep onset latency (zolpidem immediate-release, zaleplon, and ramelteon) and/or sleep maintenance (temazepam, flurazepam, zolpidem extended-release, eszopiclone, and low-dose doxepin). However, during their administration, N3 sleep and REM sleep do not regain normal lev-

els or can be even further reduced. With respect to suvorexant, the compound increases N2 sleep and REM sleep in patients with insomnia disorder (Monti et al., 2015b).

Hypersomnia disorder is a term used for a group of disorders in which the primary characteristic is excessive daytime sleepiness in the presence of normal or longer than normal nocturnal sleep (Larson-Prior et al., 2014). Among these disorders, the most common is narcolepsy. The management of this pathology includes several behavioral approaches and pharmacological treatment. For excessive daytime sleepiness, modafinil is in the first line pharmacological treatment. This drug blocks the dopamine transporter (DAT) and increases dopamine synaptic levels, which is central in its wake-promoting effect; in fact, genetic ablation of the DAT abolishes the wake-promoting effect of modafinil. However, there are other possible sites of action of this drug (Wisor, 2013). Amphetamine-like drugs such as methylphenidate are also used to reduce sleepiness.

Parasomnias are unpleasant or undesirable behavioral phenomena that occur during the sleep period. There are different types of parasomnias (Pandi-Perumal et al., 2014). One of them is the REM sleep behavioral disorder (RBD). During RBD, the REM sleep atonia does not occur and the patients act out their dreams. Severe lesions can occur during the REM without atonia episodes. About 90% of patients with chronic RBD respond well to clonazepam (0.5–2 mg) administered half an hour before sleep time (Mahowald and Schneck, 2009). Clonazepam is a BDZ whose mechanism of action for the RBD is still unknown.

1.8. CONCLUSIONS AND FUTURE DIRECTIONS

A detailed knowledge of the anatomy and physiology of the activating and hypnogenic systems is important to understand and treat sleep pathologies. A recent achievement in relation to the activating systems has been the unveiling of the pathogenesis of narcolepsy. This pathology is caused by the degeneration of hypocretinergic neurons (Mignot, 2011), which prompted paraclinical studies such as the titration of hypocretin-1 in the cerebrospinal fluid for diagnostic confirmation of narcolepsy, and therapeutic advances such as intranasal hypocretin-1 administration for the treatment of some aspects of the disease (Baier et al., 2008).

KEYWORDS

- **REM**
- **reticular formation**
- **hypothalamus**
- **basal forebrain**
- **sleep**
- **MCH**
- **acetylcholine**
- **dopamine**
- **hypocretin**
- **histamine**
- **norepinephrine**
- **serotonin**

REFERENCES

American Academy of Sleep Medicine. *International Classification of Sleep Disorders: Diagnostic and Coding Manual*; Westchester, IL, 2005.

Aston-Jones, G.; Bloom, F. E. Activity of Norepinephrine-Containing Locus Coeruleus Neurons in Behaving Rats Anticipates Fluctuations in the Sleep-Waking Cycle. *J. Neurosci.* **1981,** *1,* 876–886.

Baier, P. C.; Weinhold, S. L.; Huth, V.; Gottwald, B.; Ferstl, R.; Hinze-Selch, D. Olfactory Dysfunction in Patients with Narcolepsy with Cataplexy is Restored by Intranasal Orexin A (Hypocretin-1). *Brain*. **2008,** *131,* 2734–2741.

Basheer, R.; Strecker, R. E.; Thakkar, M. M.; McCarley, R. W. Adenosine and Sleep-Wake Regulation. *Prog. Neurobiol.* **2004,** *73,* 379–396.

Belardetti, F.; Borgia, R.; Mancia, M. Prosencephalic Mechanisms of ECoG Desynchronization in Cerveau Isole Cats. *Electroencephalogr. Clin. Neurophysiol.* **1977,** *42,* 213–225.

Benedetto, L.; Chase, M.; Torterolo, P. GABAergic Processes Within the Median Preoptic Nucleus Promote NREM Sleep. *Behav. Brain Res.* **2012,** *232,* 60–65.

Benedetto, L.; Rodriguez-Servetti, Z.; Lagos, P.; D'Almeida, V.; Monti, J. M.; Torterolo, P. Microinjection of Melanin Concentrating Hormone into the Lateral Preoptic Area Promotes non-REM Sleep in the Rat. *Peptides.* **2013,** *39C,* 11–15.

Berridge, C. W.; Abercrombie, E. D. Relationship between Locus Coeruleus Discharge Rates and Rates of Norepinephrine Release within Neocortex as Assessed by in vivo Microdialysis. *Neuroscience.* **1999,** *93,* 1263–1270.

Bittencourt, J. C.; Presse, F.; Arias, C.; Peto, C.; Vaughan, J.; Nahon, J. L. Vale, W. Sawchenko, P. E. The Melanin-Concentrating Hormone System of the Rat Brain: An Immuno- and Hybridization Histochemical Characterization. *J. Comp. Neurol.* **1992,** *319,* 218–245.

Borbely, A. A. A Two Process Model of Sleep Regulation. *Hum. Neurobiol.* **1982,** *1,* 195–204.

Boucetta, S.; Cisse, Y.; Mainville, L.; Morales, M.; Jones, B. E. Discharge Profiles across the Sleep-Waking Cycle of Identified Cholinergic, GABAergic, and Glutamatergic Neurons in the Pontomesencephalic Tegmentum of the Rat. *J. Neurosci.* **2014,** *34,* 4708–4727.

Bremer, F. Cerveau "Isole" et Physiologie du Sommeil. *C. R. Soc. Biol.* **1935,** *118,* 1235–1241.

Cape, E. G.; Jones, B. E. Effects of Glutamate Agonist Versus Procaine Microinjections into the Basal Forebrain Cholinergic Cell Area Upon Gamma and Theta Eeg Activity and Sleep-Wake State. *Eur. J. Neurosci.* **2000,** *12,* 2166–2184.

Chase, M. H. Motor Control during Sleep and Wakefulness: Clarifying Controversies and Resolving Paradoxes. *Sleep Med. Rev.* **2013,** *17,* 299–312.

Coyle, J. T.; Price, D. L.; DeLong, M. R. Alzheimer's Disease: A Disorder of Cortical Cholinergic Innervation. *Science.* **1983,** *219,* 1184–1190.

Curro Dossi, R.; Pare, D.; Steriade, M. Short-Lasting Nicotinic and Long-lasting Muscarinic Depolarizing Responses of Thalamocortical Neurons to Stimulation of Mesopontine Cholinergic Nuclei. *J. Neurophysiol.* **1991,** *65,* 393–406.

de Lecea, L.; Kilduff, T. S.; Peyron, C.; Gao, X.; Foye, P. E.; Danielson, P. E.; Fukuhara, C.; Battenberg, E. L.; Gautvik, V. T.; Bartlett, F. S.; 2nd, Frankel, W. N.; van den Pol, A. N.; Bloom, F. E.; Gautvik, K. M.; Sutcliffe, J. G. The Hypocretins: Hypothalamus-Specific Peptides with Neuroexcitatory Activity. *Proc. Natl Acad. Sci. U S A*. **1998,** *95,* 322–327.

Dement, W.; Kleitman, N. The Relation of Eye Movements during Sleep to Dream Activity: An Objective Method for the Study of Dreaming. *J. Exp. Psychol.* **1957,** *53,* 339–346.

Devera, A.; Pascovich, C.; Lagos, P.; Falconi, A.; Sampogna, S.; Chase, M. H.; Torterolo, P. Melanin-Concentrating Hormone (MCH) Modulates the Activity of Dorsal Raphe Neurons. *Brain Res.* **2015,** *1598,* 114–128.

Dringenberg, H. C.; Vanderwolf, C. H. Neocortical Activation: Modulation by Multiple Pathways Acting on Central Cholinergic and Serotonergic Systems. *Exp. Brain. Res.* **1997,** *116,* 160–174.

Feenstra, M. G. Dopamine and Noradrenaline Release in the Prefrontal Cortex in Relation to Unconditioned and Conditioned Stress and Reward. *Prog. Brain Res.* **2000,** *126,* 133–163.

Foote, S. L.; Berridge, C. W.; Adams, L. M.; Pineda, J. A. Electrophysiological Evidence for the Involvement of the Locus Coeruleus in the Alerting, Orienting, and Attending. In *Progress in Brain Research;* Barnes, C. D., Pompeiano, O., Eds.; Elsevier: Amsterdam, 1991; vol.88, pp 521–531.

Gallopin, T.; Fort, P.; Eggermann, E.; Cauli, B.; Luppi, P. H.; Rossier, J.; Audinat, E.; Muhlethaler, M.; Serafin, M. Identification of Sleep-Promoting Neurons in vitro. *Nature.* **2000,** *404,* 992–995.

Gillin, J. C.; Sitaram, N. Rapid Eye Movement (REM) Sleep: Cholinergic Mechanisms. *Psychol. Med.* **1984,** *14,* 501–506.

Huang, Z. L.; Urade, Y.; Hayaishi, O. The Role of Adenosine in the Regulation of Sleep. *Curr. Top. Med. Chem.* **2011,** *11,* 1047–1057.

Jacobs, B. L.; Azmitia, E. C. Structure and Function of the Brain Serotonin System. *Physiol. Rev.* **1992,** *72,* 165–229.

Jacobs, B. L.; Fornal, C. A. Brain Serotonergic Neuronal Activity in Behaving Cats. In *Serotonin and Sleep: Molecular, Functional and Clinical Aspects;* Monti, J. M. et al., Eds.*;* Birkhauser, Basel: Boston, Berlin, 2008.

Jones, B. Reticular Formation: Cytoarchitecture, Transmitter and Projections. In *The Rat Nervous System;* Paxinos, G., Ed.*;* Academic Press: San Diego, CA, 1995; 2nd ed., pp 155–171.

Jones, B. Basic Mechanisms of Sleep-Wake States. In *Principles and Practices of Sleep Medicine;* Kryger, M. H. et al., Eds.; Elsevier-Saunders: Philadelphia, 2005, pp 136–153.

Kalivas, P. W. Histamine-Induced Arousal in the Conscious and Pentobarbital-Pretreated Rat. *J. Pharmacol. Exp. Ther.* **1982,** *222,* 37–42.

Kiyashchenko, L. I.; Mileykovskiy, B. Y.; Maidment, N.; Lam, H. A.; Wu, M. F.; John, J.; Peever, J.; Siegel, J. M. Release of Hypocretin (Orexin) during Waking and Sleep States. *J. Neurosci.* **2002,** *22,* 5282–5286.

Kumar, V. M. Why the Medial Preoptic Area is Important for Sleep Regulation. *Indian J. Physiol. Pharmacol.* **2004,** *48,* 137–149.

Lagos, P.; Monti, J. M.; Jantos, H.; Torterolo, P. Microinjection of the Melanin-Concentrating Hormone into the Lateral Basal Forebrain Increases REM Sleep and Reduces Wakefulness in the Rat. *Life Sci.* **2012,** *90,* 895–899.

Lagos, P.; Torterolo, P.; Jantos, H.; Chase, M. H.; Monti, J. M. Effects on Sleep of Melanin-Concentrating Hormone Microinjections into the Dorsal Raphe Nucleus. *Brain Res.* **2009,** *1265,* 103–110.

Lagos, P.; Urbanavicius, J.; Scorza, C.; Miraballes, R.; Torterolo, P. Depressive-Like Profile Induced by MCH Microinjections into the Dorsal Raphe Nucleus Evaluated in the Forced Swim Test. *Behav. Brain Res.* **2011,** *218,* 259–66.

Larson-Prior, L. J.; Ju, Y. E.; Galvin, J. E. Cortical-Subcortical Interactions in Hypersomnia Disorders: Mechanisms Underlying Cognitive and Behavioral Aspects of the Sleep-Wake Cycle. *Front. Neurol.* **2014,** *5,* 165.

Lee, M. G.; Hassani, O. K.; Alonso, A.; Jones, B. E. Cholinergic Basal Forebrain Neurons Burst with Theta During Waking and Paradoxical Sleep. *J. Neurosci.* **2005a,** *25,* 4365–4369.

Lee, M. G.; Hassani, O. K.; Jones, B. E. Discharge of Identified Orexin/Hypocretin Neurons across the Sleep-Waking Cycle. *J. Neurosci.* **2005b,** *25,* 6716–6720.

Lindsley, D. B.; Schreiner, L. H.; Knowles, W. B.; Magoun, H. W. Behavioral and Eeg Changes Following Chronic Brain Stem Lesions in the Cat. *Electroencephalogr. Clin. Neurophysiol.* **1950,** *2,* 483–498.

Lopez Hill, X.; Pascovich, C.; Urbanavicius, J.; Torterolo, P., Scorza, C. The Median Raphe Nucleus Participates in the Depressive-Like Behavior Induced by MCH: Differences with the Dorsal Raphe Nucleus. *Peptides.* **2013,** 50C, 96–99.

Lu, J.; Sherman, D.; Devor, M.; Saper, C. B. A Putative Flip-Flop Switch for Control of REM Sleep. *Nature.* **2006,** *441,* 589–594.

Luppi, P. H.; Gervasoni, D.; Verret, L.; Goutagny, R.; Peyron, C.; Salvert, D.; Leger, L.; Fort, P. Paradoxical (REM) Sleep Genesis: The Switch from an Aminergic-Cholinergic to a GABAergic-Glutamatergic Hypothesis. *J. Physiol. Paris.* **2007,** *100,* 271–283.

Mahowald, M. W.; Schneck, C. REM Sleep Parasomnias. In *Principles and Practices of Sleep Medicine;* Kryger, M. H. et al., Eds.*;* Elsevier-Saunders: Philadelphia, 2009, pp 1083–1097.

Marrosu, F.; Portas, C.; Mascia, M. S.; Casu, M. A.; Fa, M.; Giagheddu, M.; Imperato, A.; Gessa, G. L. Microdialysis Measurement of Cortical and Hippocampal Acetylcholine Release during Sleep-Wake Cycle in Freely Moving Cats. *Brain Res.* **1995,** *671,* 329–332.

McCarley, R. W. Neurobiology of REM and NREM Sleep. *Sleep Med.* **2007,** *8,* 302–330.

McGinty, D.; Szymusiak, R. Sleep-Promoting Mechanisms in Mammals. In *Principles and Practices of Sleep Medicine;* Kryger, M. H. et al., Eds.*;* Elsevier-Saunders: Philadelphia, 2005, pp 169–184.

McGinty, D. J.; Harper, R. M. Dorsal Raphe Neurons: Depression of Firing during Sleep in Cats. *Brain Res.* **1976,** *101,* 569–575.

Mignot, E. Narcolepsy: Pathophysiology and Genetic Predisposition. In *Principles and Practices of Sleep Medicine;* Krieger, M. H. et al., Eds.*;* Saunders: Philadelphia, 2011, pp 938–956.

Mileykovskiy, B. Y.; Kiyashchenko, L. I.; Siegel, J. M. Behavioral Correlates of Activity in Identified Hypocretin/Orexin Neurons. *Neuron.* **2005,** *46,* 787–798.

Mirenowicz, J.; Schultz, W. Preferential Activation of Midbrain Dopamine Neurons by Appetitive Rather Than Aversive Stimuli. *Nature.* **1996,** *379,* 449–451.

Mistlberger, R. E. Circadian Regulation of Sleep in Mammals: Role of the Suprachiasmatic Nucleus. *Brain Res. Brain Res. Rev.* **2005,** *49,* 429–454.

Montagna, P. Fatal Familial Insomnia: A Model Disease in Sleep Physiopathology. *Sleep Med. Rev.* **2005,** *9,* 339–353.

Monti, J. M. The Role of Dorsal Raphe Nucleus Serotonergic and Non-Serotonergic Neurons, and of Their Receptors, in Regulating Waking and Rapid Eye Movement (REM) Sleep. *Sleep Med. Rev.* **2010a,** *14,* 319–327.

Monti, J. M. The Structure of the Dorsal Raphe Nucleus and Its Relevance to the Regulation of Sleep and Wakefulness. *Sleep Med. Rev.* **2010b,** *14,* 307–317.

Monti, J. M. The Role of Tuberomammillary Nucleus Histaminergic Neurons, and of Their Receptors, in the Regulation of Sleep and Waking. In *REM Sleep: Regulation and Function;* Mallick B.N., P.-P. S., McCarley R.W., Morrison A.R., Eds.*;* Cambridge University Press: Cambridge, UK, 2011, pp 223–233.

Monti, J. M.; Jantos, H. The Roles of Dopamine and Serotonin, And of Their Receptors, In Regulating Sleep and Waking. *Prog. Brain Res.* **2008,** *172,* 625–646.

Monti, J. M.; Lagos, P.; Jantos, H.; Torterolo, P. Increased REM Sleep After Intra-Locus Coeruleus Nucleus Microinjection of Melanin-Concentrating Hormone (MCH) in the Rat. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* **2015a**, *56,* 185–188.

Monti, J. M.; Monti, D. The Involvement of Dopamine in the Modulation of Sleep and Waking. *Sleep Med. Rev.* **2007,** *11,* 113–133.

Monti, J. M.; Torterolo, P.; Lagos, P. Melanin-Concentrating Hormone Control of Sleep-Wake Behavior. *Sleep Med. Rev.* **2013,** *17,* 293–298.

Monti, J. M.; Torterolo, P.; Pandi-Perumal, S. R. The Effects of Selective Serotonin 5-HT2A Receptor Antagonists and Inverse Agonists on Sleep and Wakefulness. Submitted for publication, **2015b.**

Moruzzi, G.; Magoun, H. W. Brain Stem Reticular Formation and Activation of the EEG. *Electroencephalogr. Clin. Neurophysiol.* **1949,** *1,* 455–473.

Nelson, L. E.; Lu, J., Guo, T.; Saper, C. B.; Franks, N. P.; Maze, M. The Alpha2-Adrenoceptor Agonist Dexmedetomidine Converges on an Endogenous Sleep-Promoting Pathway to Exert its Sedative Effects. *Anesthesiology*. **2003,** *98,* 428–436.

Nishino, S.; Mignot, E. Pharmacological Aspects of Human and Canine Narcolepsy. *Prog. Neurobiol.* **1997,** *52,* 27–78.

Nishino, S.; Mignot, E. Wake-Promoting Medications: Basic Mechanisms and Pharmacology. In *Principles and Practices of Sleep Medicine;* Kryger, M. H. et al. Eds.*;* Elsevier-Saunders: Philadelphia, 2005, pp 468–483.

Nishino, S.; Ripley, B.; Overeem, S.; Lammers, G. J.; Mignot, E. Hypocretin (Orexin) Deficiency in Human Narcolepsy. *Lancet.* **2000** *355,* 39–40.

Oades, R. D.; Halliday, G. M. Ventral Tegmental (A10) System: Neurobiology. 1. Anatomy and Connectivity. *Brain Res.* **1987** *434,* 117–165.

Pace-Schott, E. The Neurobiology of Dreaming. In *Principles and Practices of Sleep Medicine;* Kryger, M. H. et al., Eds.; Elsevier-Saunders: Philadelphia, 2005, pp 551–564.

Pandi-Perumal, S. R.; BaHammam, A. S.; Shapiro, C. M. Parasomnias. In *Encyclopedia of Psychopharmacology;* Stolerman, I. P., Price, L. H., Eds.*;* Springer-Verlag: Berlin, Heidelberg, 2014.

Pandi-Perumal, S. R.; Trakht, I.; Srinivasan, V.; Spence, D. W.; Maestroni, G. J.; Zisapel, N.; Cardinali, D. P. Physiological Effects of Melatonin: Role of Melatonin Receptors and Signal Transduction Pathways. *Prog. Neurobiol.* **2008,** *85,* 335–353.

Parmentier, R.; Ohtsu, H.; Djebbara-Hannas, Z.; Valatx, J. L.; Watanabe, T.; Lin, J. S. Anatomical, Physiological, and Pharmacological Characteristics of Histidine Decarboxylase Knock-Out Mice: Evidence for the Role of Brain Histamine in Behavioral and Sleep-Wake Control. *J. Neurosci.* **2002,** *22,* 7695–7711.

Piper, D. C.; Upton, N.; Smith, M. I.; Hunter, A. J. The Novel Brain Neuropeptide, Orexin-A, Modulates the Sleep-Wake Cycle of Rats. *Eur. J. Neurosci.* **2000,** *12,* 726–730.

Plourde, G.; Chartrand, D.; Fiset, P.; Font, S.; Backman, S. B. Antagonism of Sevoflurane Anaesthesia by Physostigmine: Effects on the Auditory Steady-State Response and Bispectral Index. *Br. J. Anaesth.* **2003,** *91,* 583–586.

Plum, F.; Posner, J. *The Diagnosis of Stupor and Coma.* Oxford University Press: New York, 2000.

Portas, C. M.; Bjorvatn, B.; Ursin, R. Serotonin and the Sleep/Wake Cycle: Special Emphasis on Microdialysis Studies. *Prog. Neurobiol.* **2000,** *60,* 13–35.

Roth, T.; Roehrs, T.; Koshorek, G.; Sicklesteel, J.; Zorick, F. Sedative Effects of Antihistamines. *J. Allergy Clin. Immunol.* **1987,** *80,* 94–98.

Sakurai, T.; Amemiya, A.; Ishii, M.; Matsuzaki, I.; Chemelli, R. M.; Tanaka, H.; Williams, S. C.; Richardson, J. A.; Kozlowski, G. P.; Wilson, S.; Arch, J. R.; Buckingham, R. E.; Haynes, A. C.; Carr, S. A.; Annan, R. S.; McNulty, D. E.; Liu, W. S.; Terrett, J. A.; Elshourbagy, N. A.; Bergsma, D. J.; Yanagisawa, M. Orexins and Orexin Receptors: A Family of Hypothalamic Neuropeptides and G Protein-Coupled Receptors That Regulate Feeding Behavior. *Cell.* **1998,** *92,* 573–585.

Satoh, K.; Fibiger, H. C. Cholinergic Neurons of the Laterodorsal Tegmental Nucleus: Efferent and Afferent Connections. *J. Comp. Neurol.* **1986,** *253,* 277–302.

Semba, K. Multiple Output Pathways of the Basal Forebrain: Organization, Chemical Heterogeneity, and Roles in Vigilance. *Behav. Brain Res.* **2000,** *115,* 117–141.

Siegel, J. M. REM Sleep. In *Principles and Practices of Sleep Medicine;* Kryger, M. H. et al., Eds.; Elsevier-Saunders: Philadelphia, 2011, pp 92–111.

Steriade, M.; McCormick, D. A.; Sejnowski, T. J. Thalamocortical Oscillations in the Sleeping and Aroused Brain. *Science.* **1993,** *262,* 679–685.

Szymusiak, R., Gvilia, I., McGinty, D. Hypothalamic Control of Sleep. *Sleep Med.* **2007,** *8,* 291–301.

Takahashi, K.; Lin, J. S.; Sakai, K. Neuronal Activity of Histaminergic Tuberomammillary Neurons during Wake-Sleep States in the Mouse. *J. Neurosci.* **2006,** *26,* 10292–10298.

Torterolo, P.; Benedetto, L.; Lagos, P.; Sampogna, S.; Chase, M. H. State-Dependent Pattern of Fos Protein Expression in Regionally-Specific Sites Within the Preoptic Area of the Cat. *Brain Res.* **2009a,** *1267,* 44–56.

Torterolo, P.; Chase, M. H. The Hypocretins (Orexins) Mediate the "Phasic" Components of REM sleep: A new hypothesis. *Sleep Sci.* **2014,** *7,* 19–29.

Torterolo, P.; Lagos, P.; Monti, J. M. Melanin-Concentrating Hormone (MCH): A New Sleep Factor? *Front. Neurol.* **2011a,** *2,* 1–12.

Torterolo, P.; Morales, F. R.; Chase, M. H. GABAergic Mechanisms in the Pedunculopontine Tegmental Nucleus of the Cat Promote Active (REM) Sleep. *Brain Res.* **2002a,** *944,* 1–9.

Torterolo, P.; Sampogna, S.; Chase, M. H. MCHergic Projections to the Nucleus Pontis Oralis Participate in the Control of Active (REM) Sleep. *Brain Res.* **2009b,** *1268,* 76–87.

Torterolo, P.; Sampogna, S.; Chase, M. H. A Restricted Parabrachial Pontine Region is Active During Non-Rapid Eye Movement Sleep. *Neuroscience.* **2011b,** *190,* 184–193.

Torterolo, P.; Sampogna, S.; Morales, F. R.; Chase, M. H. Gudden's Dorsal Tegmental Nucleus is Activated in Carbachol-Induced Active (REM) Sleep and Active Wakefulness. *Brain Res.* **2002b,** *944,* 184–189.

Torterolo, P.; Sampogna, S.; Morales, F. R.; Chase, M. H. MCH-Containing Neurons in the Hypothalamus of the Cat: Searching For a Role in the Control of Sleep and Wakefulness. *Brain Res.* **2006,** *1119,* 101–114.

Torterolo, P.; Vanini, G. Involvement of GABAergic Mechanisms in the Laterodorsal and Pedunculopontine Tegmental Nuclei (LDT-PPT) in the Promotion of REM Sleep. In *GABA and Sleep: Molecular, Functional and Clinical Aspects;* Monti, J. et al., Eds.; Springer: Basel, 2010, pp 213-231.

Torterolo, P.; Vanini, G.; Cabrera, G.; Chase, M.; Falconi, A. Hypocretins (Orexins) in the Inferior Colliculus: Anatomy and Physiology. *Sleep Med.* **2009c,** *10,* S61.

Torterolo, P.; Yamuy, J.; Sampogna, S.; Morales, F. R.; Chase, M. H. GABAergic Neurons of the Cat Dorsal Raphe Nucleus Express C-Fos During Carbachol-Induced Active Sleep. *Brain Res.* **2000,** *884,* 68–76.

Torterolo, P.; Yamuy, J.; Sampogna, S.; Morales, F. R.; Chase, M. H. GABAergic Neurons of the Laterodorsal and Pedunculopontine Tegmental Nuclei of the Cat Express C-Fos During Carbachol-Induced Active Sleep. *Brain Res.* **2001a,** *892,* 309–319.

Torterolo, P.; Yamuy, J.; Sampogna, S.; Morales, F. R.; Chase, M. H. Hypothalamic Neurons that Contain Hypocretin (Orexin) Express C-Fos during Active Wakefulness and Carbachol-Induced Active Sleep. *Sleep Res.* **2001b,** Online *4,* 25–32. http://www.sro.org/2001/Torterolo/2025.

Torterolo, P.; Yamuy, J.; Sampogna, S.; Morales, F. R.; Chase, M. H. Hypocretinergic Neurons are Primarily Involved in Activation of the Somatomotor System. *Sleep.* **2003,** *1,* 25–28.

Trachsel, L.; Tobler, I.; Achermann, P.; Borbely, A. A. Sleep Continuity and the REM-NonREM Cycle in the Rat under Baseline Conditions and After Sleep Deprivation. *Physiol. Behav.* **1991,** *49,* 575–580.

Urbanavicius, J.; Lagos, P.; Torterolo, P.; Scorza, C. Pro-Depressive Effect Induced by Microinjections of MCH into the Dorsal Raphe: Time-Course, Dose-Dependence, Effects on Anxiety-Related

Behaviors and Reversion by Nortriptyline. *Behav. Pharmacol.* **2014,** *25,* 316–324.

Vanini, G.; Torterolo, P.; McGregor, R.; Chase, M. H.; Morales, F. R. GABAergic Processes in the Mesencephalic Tegmentum Modulate the Occurrence of Active (Rapid Eye Movement) Sleep in Guinea Pigs. *Neuroscience.* **2007,** *145,* 1157–1167.

Vanini, G.; Watson, C. J.; Lydic, R.; Baghdoyan, H. A. Gamma-Aminobutyric Acid-Mediated Neurotransmission in the Pontine Reticular Formation Modulates Hypnosis, Immobility, and Breathing during Isoflurane Anesthesia. *Anesthesiology.* **2008,** *109,* 978–988.

Verret, L.; Goutagny, R.; Fort, P.; Cagnon, L.; Salvert, D.; Leger, L.; Boissard, R.; Salin, P.; Peyron, C.; Luppi, P. H. A Role of Melanin-Concentrating Hormone Producing Neurons in the Central Regulation of Paradoxical Sleep. *BMC Neurosci.* **2003,** *4,* 19.

Vitiello, M. V.; Borson, S. Sleep Disturbances in Patients with Alzheimer's Disease: Epidemiology, Pathophysiology and Treatment. *CNS Drugs.* **2001,** *15,* 777–796.

Wisor, J. Modafinil as a Catecholaminergic Agent: Empirical Evidence and Unanswered Questions. *Front. Neurol.* **2013,** *4,* 139.

Wolff, K.; Winstock, A. R. Ketamine : From Medicine to Misuse. *CNS Drugs.* **2006,** *20,* 199–218.

Xi, M. C.; Morales, F. R.; Chase, M. H. Evidence that Wakefulness and REM Sleep are Controlled by a GABAergic Pontine Mechanism. *J. Neurophysiol.* **1999,** *82,* 2015–2019.

2

NEUROENDOCRINOLOGY OF SLEEP AND WAKEFULNESS

Georges Copinschi *

2.1. INTRODUCTION

Sleep involves two states of distinct brain activity: rapid eye movement (REM) sleep, and non-REM sleep. Sleep is normally initiated by light non-REM stages (stages 1 and 2), followed by a deeper non-REM stage (stage 3, also called slow-wave sleep, SWS), then by REM sleep. In healthy young subjects, this cycle, which lasts around 90 min, is generally repeated 4–6 times per night. As the night progresses, non-REM sleep becomes shallower, the duration of REM episodes becomes longer, and the number and the duration of transient awakenings increase. Aging is rapidly associated with marked alterations in sleep architecture. SWS is already markedly reduced in healthy subjects 35 years old. Thereafter, REM sleep progressively declines, in mirror image of an equivalent increase in time spent awake.[1]

Circulating hormonal levels undergo pronounced temporal oscillations, providing the endocrine system with remarkable flexibility. The temporal organization of hormonal secretions results from the interaction of two time-keeping mechanisms in the central nervous system, the *circadian pacemaker* and the *sleep–wake homeostasis*. The circadian pacemaker, or circadian clock, located in the suprachiasmatic nucleus of the hypothalamus, totally or partially controls the timing and the intensity of most hormonal circadian rhythms. In addition, it regulates the timings of sleep onset and sleep offset and the distribution

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of REM sleep. The sleep–wake homeostasis, a mechanism relating the timing and the architecture of sleep to the duration of prior wakefulness, controls the non-REM sleep, in particular SWS, and regulates, at least partially, the timing and the intensity of virtually all endocrine–metabolic systems. Conversely, hormones may modulate sleep architecture. Thus, bidirectional interrelations are operative between sleep and endocrine function.[2] The mechanisms of those sleep–endocrine interactions, which markedly differ from one hormone to another, will be reviewed in the following sections.

2.2. GROWTH HORMONE

Hormone Primarily Controlled by the Sleep–Wake Homeostasis

Pituitary growth hormone (GH) secretion is stimulated by hypothalamic GH-releasing hormone (GHRH) and inhibited by somatostatin. In addition, the acylated form of ghrelin (a peptide principally produced by the stomach) also stimulates GH secretion. In adults, the normal 24 h profile of circulating GH levels consists of stable low levels abruptly interrupted by secretory pulses. In young healthy adults, the most reproducible GH secretory pulse is consistently observed shortly after sleep onset and is temporally and quantitatively related to SWS. As illustrated in Figure 2.1, this sleep-onset pulse is generally the largest GH pulse over the 24 h span in adult males, while high amplitude daytime pulses are frequent in young adult females.[3,4]

A sleep-onset associated GH pulse is still observed when sleep is delayed or advanced.[5–8] Therefore, shifts of the sleep–wake cycle are always associated with parallel shifts of GH secretion (Fig. 2.2). Conversely, GH secretion during the sleep period is inhibited by transitional awakenings and sleep fragmentation.[9] In night workers, the most important GH secretory pulse is generally observed during the first part of the shifted sleep period.[10]

In healthy young adults, GHRH injection, when given at a time of decreased sleep propensity at a dose eliciting a GH secretory response within the physiological range, was shown to dramatically reduce the duration of awakenings, to markedly stimulate SWS (Fig. 2.3), and possibly, though to lesser extent, to stimulate REM sleep.[11] Animal studies indicate that the effects of GHRH on SWS are not mediated by GH, while GHRH effects on REM sleep are probably mediated by GH.[12–14] In addition, administration of ritanserin (a selective 5HT2 antagonist) or of gamma-hydroxybutyrate (GHB; a naturally occurring metabolite of GABA used in the treatment of narcolepsy) results in highly correlated simultaneous stimulations of nocturnal GH secretion and of SWS.[6,15] Thus, a robust, though complex, interaction exists between sleep and GH secretion, and sleep is clearly the major determinant of GH secretion. However, there is also some evidence for the existence of a minor circadian modulation of the occurrence and magnitude of GH secretory pulses.[3]

Several studies have shown that in normally cycling young women the amplitude of GH pulses is positively correlated with circulating estradiol levels.[4,16] In addition, daytime GH secretion was found to be higher during the luteal than during the follicular phase (Fig. 2.1), and this elevation correlated positively with circulating

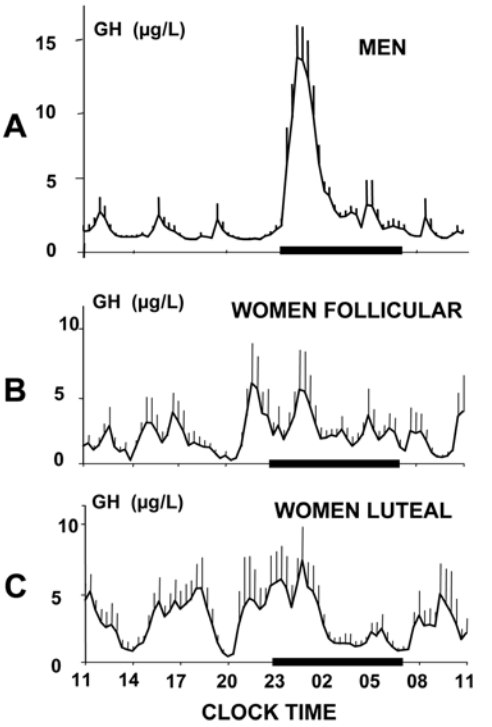

Figure 2.1: A. Mean (+ SEM) 24 h plasma growth hormone profiles in a group of 9 healthy men, aged 18–30 years. (Adapted from Van Cauter et al.[3]).
B. and C. Mean (+ SEM) 24 h plasma growth hormone profiles in a group of 10 normally cycling women, age 21–36 years, during follicular (B) and luteal (C) phase. (Data from Caufriez et al.[17]).

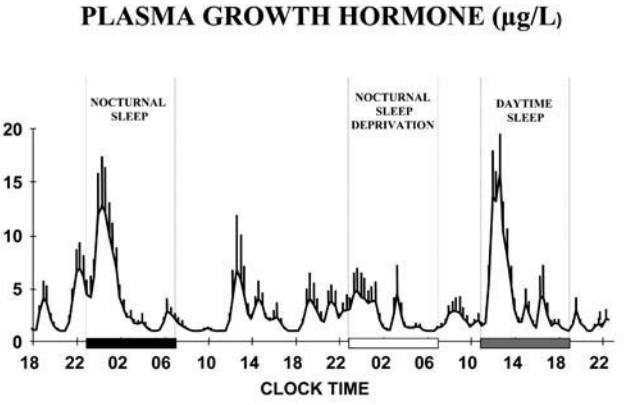

Figure 2.2: Mean (+ SEM) plasma growth hormone profiles in a group of 8 healthy men, aged 20–27 years, investigated during a 53 h period that included 8 h of nocturnal sleep, 28 h of sleep deprivation, and 8 h of daytime sleep. The black bar denotes the nocturnal sleep period, the open bar denotes the period of nocturnal sleep deprivation, and the grey bar denotes the period of daytime sleep. Blood samples were obtained at 20 min intervals. (Adapted from Van Cauter and Spiegel[100]).

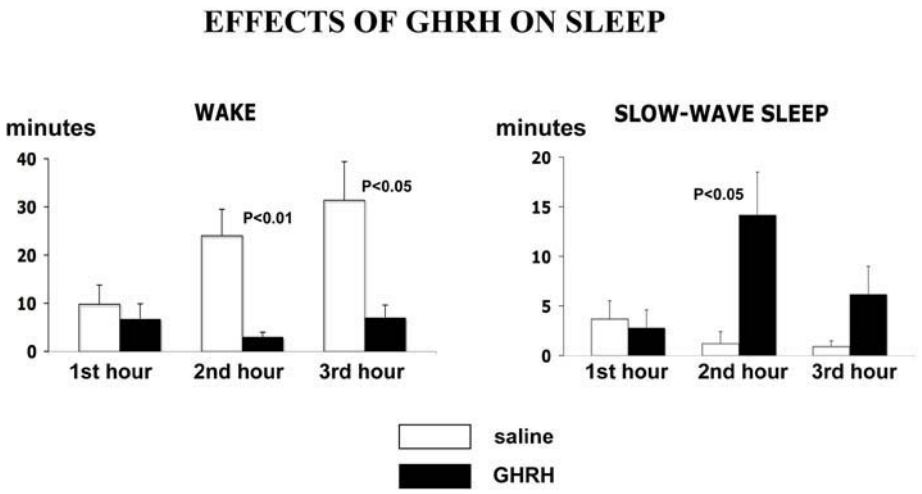

Figure 2.3: Effects of GHRH on mean (+ SEM) duration of wake and SWS in 8 healthy men, aged 24–31 years. GHRH (0.3 μg/kg body weight) was injected intravenously after 60 s of the third REM period of the sleep cycle. (Data from Kerkhofs et al.[11]).

progesterone levels (but not with estradiol levels).[17]

As illustrated in Figure 2. 4, aging is associated with dramatic parallel decreases in SWS and in GH secretion during sleep. Those age-related decreases occur in an exponential fashion between young adulthood and midlife, despite the persistence of high sex steroids levels. Thereafter, minor progressive decreases occur from midlife to old age.[1,18–20] In healthy old subjects, GH secretory profiles are similar in women and in men.[4] In postmenopausal women, progesterone administration was shown to stimulate nocturnal GH secretion, and also to prevent sleep disturbances.[21]

During pregnancy, a placental GH variant substitutes for pituitary GH to regulate maternal insulin-like growth factor-1 (IGF-1).[22,23] Interestingly, this GH variant is released by the placenta in a tonic, rather than pulsatile, fashion.[24] In acromegaly,elevated pituitary GH levels throughout the 24-h span result from a highly irregular pulsatile pattern superimposed on elevated basal levels, indicating the existence of tonic secretion.[25,26]

Because of the pulsatile nature of GH secretion, determinations of random circulating GH levels are of little or no value in the diagnosis of growth hormone disorders. Appropriate determinations of GH secretion necessarily involve multiple blood sampling collected at 15–20 min intervals for 24 h, together with polygraphic sleep recordings.

2.3. THE CORTICOTROPIC AXIS

Hormones Primarily Controlled by the Circadian Clock

Outputs from the hypothalamic suprachiasmatic nucleus activate the release of corticotropin-releasing hormone (CRH). CRH in turn stimulates pituitary secretion