Preface

The increase in our knowledge of the GABA (γ-aminobutyric acid) system in recent years has led to major advances in our understanding of sleep physiology, sleep disorders and clinical sleep medicine. The goal of this first edition is to review the major achievements made in characterizing the role of GABA in the physiology and pathology of sleep regulation and in identifying GABAergic subsystems which show potential for novel pharmacological treatments of sleep disorders.

Brain states such as sleep or waking are governed by distinct synchronized oscillatory neuronal networks which give rise to changing EEG patterns. It has increasingly been recognized that the sculpting of neuronal rhythms, the control of neuronal firing and the selection of temporary assemblies of neurons are controlled by a rich diversity of GABAergic interneurons. In addition, mutual inhibition between the brain nuclei which promote sleep and the arousal systems is known to result in switching properties that define waking and sleep states. In this process, which is driven by homeostatic and circadian influences, GABA neurons play also a significant role. The evidence reviewed in this volume clearly demonstrates that GABAergic regulatory control is at the center of sleep physiology, pathophysiology and therapeutics.

To accommodate the diverse temporal dynamics of GABAergic signaling, a corresponding diversity of GABA receptors is required on the target cells. Besides the metabotropic GABA_B receptor, the fast-responding ionotropic GABA_A receptors are of special relevance in as much as they represent the exclusive target of benzodiazepine (BZD) drugs. More recently, the discovery of GABA_A receptor subtypes, largely characterized by distinct a subunits, has opened up new opportunities for drug development. For instance, sedation, a common denominator of GABA_A receptor-related hypnotics, is mediated by a1 receptors, while a2 receptors selectively mediate the anxiolytic action of BZD.

Additionally, our understanding of the pharmacokinetic determinants (absorption rate, elimination half-life, dosage) of hypnotic drug action has progressed in parallel with the development and clinical use of a series of BDZ and non-BDZ hypnotic drugs.
The BDZ derivatives reduce sleep latency, the number of nocturnal awakenings, and wake time after sleep onset. Increases in total sleep time are related to greater amounts of stage 2 (intermediate sleep). By contrast, stage 3 and 4 sleep (deep sleep) and REM sleep (dream sleep) are decreased in patients with chronic primary insomnia and comorbid insomnia. On the other hand, the non-BZD derivatives zolpidem, zopiclone, eszopiclone and indiplon, which primarily act selectively at α1 GABA_A receptors, increase total sleep time without reducing slow wave sleep and REM sleep. Interestingly, the selective extrasynaptic GABA-receptor agonist gaboxadol increases slow wave sleep, that is, it mimics the effect of sleep deprivation.

The intricate nature of sleep regulation via the GABA system is particularly apparent in nuclei of the arousal system such as the dorsal raphe nucleus (DRN), the locus coeruleus and the pontine cholinergic system. In the DRN, local administration of the GABA_A receptor agonist muscimol increases REM sleep, whereas the local microinjection of serotonin 5-HT1B, 5-HT2A/C, and 5-HT7 receptor agonists induces the opposite effect. This result has been ascribed to the inhibition of GABAergic interneurons and the activation of long-projection GABAergic cells, respectively. GABA also plays a critical neuromodulatory role in the interaction between pontine noradrenergic and cholinergic systems. Cholinergic mechanisms are important for REM sleep induction in the pontis oralis and sublaterodorsal nuclei, and GABAergic modulation of these sites can inhibit or prevent the occurrence of REM sleep.

Organization of the First Edition

This volume is divided into three major parts. Part I: Basic Physiology and Pharmacology; Part II: Sleep Science and Circuitry; and finally, Part III. Hypnotics.

Part I consists of an overview of the basic pharmacology of the GABAergic system. The topics covered include the most recent understanding concerning the pharmacology and physiology of the GABAergic system and its receptor subtypes, the development of subtype-selective GABA_A receptor compounds for the treatment of insomnia, anxiety and epilepsy, distribution of GABA_A receptor subtypes in the human brain, and finally, the pharmacokinetic determinants of the clinical effects of benzodiazepine agonists.

Part II is the largest section in this volume and addresses the topic of sleep circuitries. These include sleep and its modulation by drugs that affect the GABA_A receptor function, subcortical neuromodulation of feedforward and feedback inhibitory microcircuits by the reticular activating system, and circadian regulation of sleep. This section also addresses the role of melatonin in sleep and the possible involvement of GABAergic mechanisms.

Part III addresses the pathophysiology of sleep disorders, differential diagnosis of insomnia, and safety and efficacy profiles of various GABAergic drugs, including zolpidem, zolpidem, eszopiclone, zaleplon, and Indiplon.

This volume is intended for pharmacologists, CNS drug discovery scientists, basic and clinical researchers, psychiatrists, and other general practitioners who...
seek an overall grasp of the physiology and clinical pharmacology of sleep. It will be helpful for medical students and graduate students of biomedical and sleep medicine specialties.

The information presented is based on the most recent sleep literature and stresses the relevance to clinical medicine and therapeutics. Information about specific drugs is occasionally repeated in several chapters throughout this volume by various authors. It is the editors’ hope that this redundancy will be construed as a benefit.

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

In summary, it is our hope that this volume will enable interested scientific and medical researchers to develop a better understanding of the science and practice of sleep medicine. We also hope that this volume will generate new ideas that lead to improvements in the care of patients who suffer from sleep disorders.

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