Introduction to the Topic

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While sleep occupies almost a third of our lives (and half or more of the lives of many animals), the processes that go on in the brain during sleep remain mysterious and in the realm of basic investigation. On the other hand, we have made enormous strides in recent years in identifying the cellular basis that underlies many of the phenomena of sleep and circadian rhythms, and in the process are beginning to frame some cogent ideas about the ultimate function of sleep. The chapters that follow in this section provide a detailed look at the basic science of sleep, from the perspectives of anatomy, physiology, pharmacology, and behavior.

Our understanding of the basic brain circuitry that regulates sleep and wakefulness has advanced considerably in recent years and continues to grow as this work remains at the cutting edge of the field [1, 2]. Although the outlines of the classic cholinergic and monoaminergic wake-promoting systems have been known since the 1980s, studies that have placed lesions in these pathways have demonstrated disappointingly little effect on amounts of baseline wake–sleep [3–5]. Recent studies have uncovered additional components of the ascending arousal system, including the parabrachial nucleus [6] and portions of the basal ganglia [7, 8], that have augmented our understanding of it and have added new pieces to the puzzle.

Similarly, our understanding of the sleep-promoting circuitry of the brain has progressed enormously in recent years. In addition to the contribution of the ventrolateral preoptic nucleus to causing sleep [2], evidence has emerged for the role of the median preoptic nucleus in accumulating sleep need [9]. Other neurons in the nucleus accumbens and in the parafacial zone in the medulla have been described [8, 10, 11], which also appear to promote sleep. Sleep-active neurons that are putatively inhibitory have been identified in the cerebral cortex [12] as well as the melanin-concentrating hormone cell group in the lateral hypothalamus [13, 14]. Their respective roles in sleep promotion are only now being explored.

There have also been major gains in our understanding of both the homeostatic and circadian regulation of sleep. Studies have uncovered the role of adenosine in causing sleepiness [15] and have identified the site in the nucleus accumbens at which caffeine acts on A2A receptors to combat sleepiness [11]. The immune interactions with sleep promotion have also been studied, identifying the role for prostaglandin D2 as a somnogen [16]. At the same time, the pathways have been worked out by which the suprachiasmatic nucleus influences wake–sleep cycles [17].

In addition to understanding the basic neuronal mechanisms that regulate sleep–wake, there has been substantial progress in understanding the interactions between sleep and a myriad of other physiological processes that it affects. These range from interactions with basic physiological systems, such as autonomic, respiratory, and immune systems [18, 19], to the effect of sleep fragmentation or loss on cognitive processes, ranging from attention to memory [20]. In particular, there is an emerging consensus that loss of specific stages of sleep may impair specific types of memory formation [21]. Understanding the cellular mechanisms that underlie this vulnerability will be critical to determining the biological function of sleep.

Finally, as our understanding of sleep neuroscience has broadened, we have come to understand how disruption of this delicate physiological mechanism can produce the range of sleep disorders that we see as clinicians. For example, the effects of stress-induced insomnia on wake–sleep circuitry support insomnia being a distinct state, neither wake nor sleep, with activation of both sleep-promoting and limbic and arousal systems at the same time [22, 23]. Our knowledge about the mechanisms of atonia during REM sleep has illuminated our understanding of both cataplexy and REM behavior disorder [24, 25]. In patients with sleep apnea, we

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are beginning to understand the arousal mechanisms that lead to frequent arousals [26], and how these interact with the control of the upper airway muscles that are necessary for ventilation.

Our ultimate goal as sleep clinicians is to improve the lot of our patients. As we better understand the diseases we treat, we are able to come up with novel therapies that are informed by the underlying pathophysiology. For example, the current development of orexin antagonists as sleep-promoting drugs is based upon our understanding of the biology of orexins and their contribution to maintaining wakefulness [27]. Conversely, the development of H3 antagonists as wake-promoting drugs depends upon our understanding of the histamine arousal system and its pharmacology [28].

The ideal situation in basic science is for our most basic observations to inform our bedside diagnosis and treatment abilities and to carry back information from the bedside that stirs the next generation of basic science questions. This has certainly been the case in the sleep field, as the chapters that follow in this basic science section demonstrate, and the ones in succeeding in the clinical sections emphasize.

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