BOOK REVIEW

Serotonin and Sleep: Molecular, Functional, and Clinical Aspects

Edited by J. M. Monti, S.R. Pandi-Perumal, B.L. Jacobs, and D. J. Nutt. Basel: Birkhäuser; 2008

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THE ROLE OF SEROTONIN IN BRAIN IS OF SPECIAL INTEREST TO SLEEP SCIENTISTS. IN ADDITION TO BEING THE TARGET OF WIDELY USED PSYCHOACTIVE drugs, serotonin was the first hypothesized sleep-promoting substance of modern neuroscience, and is among the intriguing REM-off neuromodulatory systems. The recent book, *Serotonin and Sleep: Molecular, Functional, and Clinical Aspects,* edited by Monti et al., provides the sleep community with an up-to-date source of much of what scientists have learned about the properties of serotonin-containing neurons and their effects on sleep and wakefulness.

An introductory chapter, by Ursin, provides an excellent history and overview of the evolving concept of the role of serotonin in sleep, from the early findings supporting the sleep-promoting theories of Jouvet and Koella, through the evidence that 5HT is wake-promoting. Ursin then summarizes attempts to integrate these concepts.

The neuroanatomy of the dorsal and median raphe nuclei (DR and MR), which are the origins of the serotonergic innervation of the forebrain, is reviewed in two detailed chapters. As pointed out by Lowry and colleagues, these nuclei have several subdivisions, containing several cell phenotypes, with distinctive connectivity. They define six different ascending serotonergic pathways. Vertes and Linley also emphasize the differences between the projections of the DR and MR, and show the fine details of the projection fiber distribution using serotonin transporter immunochemistry. A third anatomical chapter, by Deurveiller and Semba, summarizes what is known about the serotonergic innervation of the hypothalamic circadian and NREM sleep control pathways and how these might interact to modulate sleep-wake regulation. The effects of serotonin on circadian control are further discussed by Cardinali and colleagues, who review the effects of agonists and antagonists as well as melatonin on clock neurons, in the suprachiasmatic nucleus (SCN), and on circadian phase control. They also discuss uses of these agents in human circadian disorders.

Serotonin receptor diversity, comprising at least 14 types and more subtypes, is considered in several chapters. Hannon and Hoyer provide an excellent and detailed overview of this topic, including information about the cloning and distribution of receptors in brain, ligand specificity, and identification of human receptor genes. Importantly, they review the synaptic actions of each receptor type. They also include current views about the role of particular receptor types in specific human disease susceptibility and treatment. Santana and colleagues provide additional detailed information about the distribution of receptor types in brain, including neocortex, emphasizing what is known about the neuronal phenotypes that express certain receptors, and species differences in receptor density.

The specificity of the actions of drugs is determined by their receptor affinities. Several chapters focus on the role of specific receptor types in sleep-wake regulation, as shown by administration of drugs with specific receptor affinities. Portas and Gronli summarize knowledge of the effects on sleep of drugs affecting $5HT_{1A}$ and $5HT_{1B}$ receptors, which have both postsynaptic and presynaptic loci, the later including inhibitory autoreceptors on serotonin neurons, themselves. This chapter, and that by Monti and Jantos, compare the effects of systemic and local DR administration of $5HT_{1A/B}$ receptor agonists and antagonists, on REM. Kitka and Bagdy review studies of effects on sleep of drugs binding to $5HT_{2A/2B/2C}$ receptors, noting that some antagonists can increase NREM sleep, and that atypical anti-psychotic drugs have affinity to this class receptors.

Staner and colleagues review studies of the $5HT_3$ receptor, the only receptor directly controlling an ion channel. They note that $5HT_3$ receptor antagonists are used in humans to help control migraine and other types of pain as well as nausea. The biology of excitatory $5HT_7$ receptors is reviewed by Thomas, noting their localization both in DR and the SCN, among many targets. Adrien provides an important contribution, summarizing the sleep-wake changes resulting from "knock out" of $5HT_{1A}$, $5HT_{1B}$, $5HT_{2A}$, $5HT_{2C}$, and $5HT_7$ receptors, as well as the 5HT transporter and monoamine oxidase in mice. The findings are complex, but do support the role of $5HT_{1A,}$ $5HT_{1B}$, and $5HT_7$ receptors in REM control.

Regulation of serotonin neuronal activity is reviewed in several chapters. Jacobs and Fornal describe their extensive series of studies showing that medullary serotonin-containing neurons are activated during locomotion and enhanced respiratory drive, but not in association with sympathetic activation. A minor subset of DR neurons exhibit enhanced discharge in association with rhythmic motor activity, such as grooming, and elevated muscle tone. These authors speculate that serotonin neuronal activity allows the brain to coordinate motor, autonomic, and sensory processes. This remains the strongest hypothesis that integrates the REM-off and waking behavior of serotonin neurons.

Sakai further characterizes the subtypes of DR and medullary putative serotonergic neurons and describes studies assessing the regulation of DR neuronal activity across the sleep wake

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cycle. He hypothesizes that suppression that DR serotoninergic neuronal discharge in REM results from withdrawal of excitatory input. However, the studies reported in the chapter by Luppi and colleagues suggest that GABAergic inhibition suppresses DR discharge in REM. Auerbach describes additional studies of the regulation of neuronal activity and serotonin release in the DR by GABAergic and glutamatergic agonists and antagonists. A chapter by Sinton nicely reviews biology of the orexin/hypocretin system and the direct and indirect mechanisms underlying modulation of DR neurons by orexin. Then, Sanford and colleagues review the pontine mechanisms underlying the inhibitory regulation of REM by serotonin. They also review evidence for facilitation of REM by the amygdala, and evidence that the inhibitory effects of serotonin on REM may be mediated, in part, through the amygdala.

The possible role of serotonin in human sleep disorders is considered in several chapters. Buchanan and colleagues first summarize evidence that medullary serotonin neurons are CO_2-sensitive and that serotonin facilitates respiratory responses to hypercapnia. They review evidence for abnormalities in serotonin neurons associated with Sudden Infant Death syndrome, obstructive sleep apnea, and panic disorder. Veasey further reviews mechanisms underlying effects of serotonin on respiratory control, and summarizes studies examining effects of serotonergic drugs on human obstructive sleep apnea as well as the bulldog model of obstructive sleep apnea.

Argyropoulos and colleagues review effects of serotonin agonists and serotonin-reuptake inhibitors (SSRIs) in humans, including studies of both depressed patients and normal volunteers. Both types of drugs usually increase REM onset latency and increase sleep fragmentation, in general agreement with animal studies. Winokur and Kamath provide an overview of sleep abnormalities associated with schizophrenia, and the effects of antipsychotic drugs, pointing out that many such drugs block $5HT_{2A}$ as well as dopamine receptors. Pace-Schott addresses available evidence on the effects of SSRIs on dreaming, and the possible relationships between REM, serotonin, and dreaming in depressed and normal subjects.

Among the important strengths of this book is the fact that most authors provide a thorough review of the literature in their topic, rather than only summarizing their own work. Bibliographies are very extensive. Thus, the book is an invaluable resource, strongly recommended to all investigators in the area of sleep neurobiology. Minor weaknesses include overlap of content in some chapters, and lack of chapters on the cellular neurobiological effects of serotonin and a full explication of studies of the McCarley-Hobson model. I believe that, in the end, a full understanding of the effects of serotonin, the connections between its many wake functional effects, REM-off behavior, and its potency in treatment of depression and related disorders, will lead us to far greater understanding of sleep, itself. This comprehensive book contributes to the goal.

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