Published online: May 28, 2021

Steiner MA, Yanagisawa M, Clozel M (eds): The Orexin System. Basic Science and Role in Sleep Pathology. Front Neurol Neurosci. Basel, Karger, 2021, vol 45, pp IX–X (DOI: 10.1159/000514968)

Preface

Orexins (hypocretins) and their receptors were discovered in 1998. Orexin neuropeptides are produced by a very small number of cells in the lateral hypothalamus, suggesting a fundamental role in homeostasis. Despite the name "orexin," which was coined after the original discovery of its role in appetite regulation, the orexin system has foremost emerged as a crucial player in the maintenance of wakefulness and vigilance. The orexin system is highly conserved across vertebrates; its role in arousal and wakefulness stabilization is essential and cannot be replaced by another brain circuit. The discovery of hypocretin/orexin rapidly led to the hypothesis of its pathogenic contribution in the abnormal state of hyperarousal of insomnia and, for its deficiency, in narcolepsy and cataplexy.

Sleep is one of the greatest marvels and mysteries of our physiology. Sleep is fundamental to our daily life and the quality of our aging. Sleep deprivation alters learning and memory and immune cell activity, increases the risk of hypertension, cancer, and depression and increases amyloid-β concentration in the brain. Sleep helps to repair DNA strand breaks and synaptic disruptions that occur during the active period and controls sympathetic tone. Conversely, insomnia is a major disease in our modern world, and sleep is itself frequently affected by diseases. Insomnia is one of the first symptoms of Alzheimer's disease. Short sleep duration predicts higher all-cause mortality.

The discovery of the orexin system opened the door to a novel and dynamic research on sleep. It is this research which we wish to honor here, within this book. Since this discovery, pharmaceutical companies started to develop molecules to enhance the understanding of the consequences of orexin receptor blockade in insomnia. In 2007, researchers at Actelion Pharmaceuticals Ltd. described, for the first time, the sleep-promoting effects of a dual orexin receptor antagonist (DORA), almorexant, across several species, including human. In 2014 and 2019, respectively, the US Food and Drug Administration (FDA) approved the two DORAs, suvorexant and lemborexant, for the treatment of primary insomnia. A third molecule, daridorexant, improved not only sleep but also daytime functioning in patients with insomnia, and, as we publish this book, is under review for approval by health authorities. These three DORAs are all efficacious in reducing latency to sleep and wake after sleep onset, and they prolong total sleep time without altering the physiological sleep architecture.

Besides stabilizing wakefulness, other roles of orexins are emerging, including the modulation of stress-, feeding-, and reward-related pathways within the brain. This functional diversity is for a large part achieved through the complexity of the orexin system, with its two different peptides and two receptors that are differentially released and distributed throughout the brain. The first selective orexin 1 or 2 receptor antagonists (SORAs) have entered clinical trials and are currently under investigation for the treatment of mood, anxiety, and eating disorders. Orexin receptor agonists are being explored as novel treatments for narcolepsy.

In this book, *The Orexin System. Basic Science and Role in Sleep Pathology*, we have gathered the ideas and perspectives from some of the most influential researchers in the fields of hypocretin/orexin and sleep. As authors, they share their thoughts on novel developments and provide focused reviews on topics of particular interest.

In the first section of the book, "The Orexin System and Its Role in Regulating Sleep and Wake," Professors Luis de Lecea, Takeshi Sakurai & Masashi Yanagisawa, Thomas S. Kilduff, and Stuart M. Fogel, take you on a journey to illustrate the complexity and intercorrelation of the orexin system with other sleep- and wake-regulating neurotransmitter systems. The authors explain the intricate role of the orexin system in the different sleep phases and in the pathways that are, for instance, related to memory and cognition.

In the second section, "Cellular and Molecular Dissection of the Orexin System," Professors Denis Burdakov, Lior Appelbaum, Antoine R. Adamantidis, and Jyrki P. Kukkonen, marvel at the cellular and subcellular diversity of the few thousand orexin-producing neurons within the hypothalamus. The temporally controlled firing of orexin neurons and the spatially restricted actions within certain projection areas can be explained by the diversity in orexin receptor signaling pathways, the co-release of other types of neurotransmitters, the integration of multiple incoming signals, and the assortments of different gene-expression profiles among clusters of orexin neurons.

In the final section of the book, "The Orexin System in Sleep Pathology," Professors Emmanuel Mignot, Gary Aston-Jones, Janet M. Mullington, and Yves Dauvilliers provide an overview of diseases which are caused by, or associated with, a dysfunctional orexin system, such as narcolepsy, insomnia, substance abuse, or Alzheimer's disease. They invite us to explore the new potential therapeutic applications derived from research around the orexin system.

We, as editors, wish to acknowledge with gratitude the many scientists, clinicians, and patients who have contributed towards the development of the understanding of the orexin system and the clinical applications to improving the health of patients and the community. We invite the reader to now take a "deep dive" into the mysterious world of this fascinating hypocretin/orexin system, which lies at the core of the sleep and wake state regulation inside our brain. We hope you will find the chapters as thought-provoking and informative as we have.

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