

PREFACE

Orexin/hypocretin research began in 1998, as a result of the discovery of a new hypothalamic neuropeptide. In 1999, it was found that mutations in the orexin/hypocretin-related genes caused a sleep disorder (narcolepsy) in dogs and mice. These findings were soon followed by the discoveries of orexin/hypocretin ligand deficiency in human narcolepsy.

The finding of the major pathophysiological mechanisms of human narcolepsy resulted in its reclassification as a neurological, not a psychiatric, disorder. The importance of early diagnosis and initiation of treatment for human narcolepsy has been repeatedly emphasized because the disease typically starts around puberty (when social and school influences become important). Orexin/hypocretin deficiency in narcolepsy subjects can be detected clinically in cerebrospinal fluid (CSF) orexin/hypocretin measures (low CSF orexin/hypocretin levels are strongly associated with narcolepsy–cataplexy among various neurologic and sleep disorders). Thus, the CSF orexin/hypocretin measurements are expected to be included as a diagnostic test for narcolepsy–cataplexy in the second revision of international diagnostic criteria (ICSD). This positive diagnostic test is very useful for establishing an early diagnosis for narcolepsy–cataplexy, and many patients will likely receive immediate benefits. Cerebrospinal orexin/hypocretin measurements are also informative for the nosological classification of hypersomnia. Because orexin/hypocretin deficiency is observed in most human narcolepsy–cataplexy, orexin/hypocretin replacement therapy is now a promising new choice for the treatment of human narcolepsy, and research in this area is actively in progress.

The Orexin/Hypocretin System: Physiology and Pathophysiology examines these exciting discoveries and presents new findings such as ligand replacement and gene therapies in animal models of narcolepsy. The next important step for narcolepsy research is to discover the pathological mechanisms for the loss of orexin/hypocretin neurons in humans. This information is critical to prevention or cure of the disease, and another breakthrough in this area is expected in the not too distant future.

How the orexin/hypocretin system physiologically regulates sleep and wakefulness remains largely unknown. It is not fully understood how and why the symptoms of narcolepsy occur when orexin/hypocretin neurotransmission is impaired. Sleep is a complex physiological phenomenon, and multiple systems are involved in its regulation. Because we were reluctant to request just one author to cover the roles of orexin/hypocretin in sleep regulation, we invited several contributors who are working in this field to freely discuss their opinions; as a result we could not avoid significant overlaps among these chapters. Because we did not instruct the authors to unify their hypotheses, controversies may also exist. However, there is room for readers to actively participate in these debates and to carry out the experiments to prove or disprove these hypotheses.

The orexin/hypocretin system is also of exceptional interest in neuroscience research. In addition to its involvement in vigilance control and narcolepsy, the system likely regulates various hypothalamic functions such as neuroendocrine functions, stress reactions, and autonomic functions necessary for human survival. Numerous researchers have initiated multidisciplinary approaches in order to understand the various aspects of the physiological functions of the orexin/hypocretin system. In the same way, narcolepsy is a useful disease model for understanding the link between vigilance control with other fundamental hypothalamic functions, such as regulation of feeding behavior and autonomic function. Similarly, clinical applications of orexin/hypocretin agonists and antagonists for various diseases are suggested.

We introduced several experimental methods for orexin/hypocretin research and discussed the use and limitations of these methods that are useful for the multidisciplinary approaches in the orexin/hypocretin research field, as well as for other neuropeptidergic systems.

Finally, we would like to emphasize that rapid, significant success in narcolepsy research has not been achieved without careful observations in the appropriate animal models of the disease. These approaches, which are used to study narcolepsy, will now encourage researchers to initiate genetic linkage and positional cloning experiments, as well as to generate various genetically engineered animal models. A link between orexin/hypocretin ligand deficiency and narcolepsy in orexin/hypocretin knockout mice could not have been made without excellent scientific acumen combined with a modicum of luck. Tenacious efforts by researchers, together with the application of modern technologies, made these breakthroughs possible in a timely manner.

Living in a post-genome era, the success of the orexin/hypocretin story is driving many researchers to search novel bioactive peptides and their receptors for further discoveries in physiology, and these are likely to lead to novel opportunities for clinical treatments. Orexins/hypocretins are one of the first endogenous ligands discovered for orphan G protein-coupled receptors. Since 1995, about 70 ligands and/or orphan receptors have been identified or re-recognized. There are still about 100 orphan receptors, and the search for the endogenous ligands for these receptors is actively in progress. It is therefore possible that the abnormal function of some of the unknown ligands and uncharacterized receptors are directly involved in the etiology and/or pathophysiology of several neurologic and psychiatric disorders. The study of the orexin/hypocretin system is a good example of what can be achieved.

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