Neurobiological Basis of Hypersomnia

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KEYWORDS

• Hypocretin • Narcolepsy • Suvorexant • Prostaglandin D2 • Adenosine • Cytokines
• Sleep-promoting supplement • Gene-knockout mice

KEY POINTS

- Narcolepsy is the most well-characterized hypersomnia and is caused by the degeneration of hypocretin-producing neurons in the hypothalamus, which are important for maintenance of wakefulness.
- Hypocretin receptor antagonist Suvorexant is a recently developed sleep-inducing drug but induces narcoleptic attack in wild-type mice by suppressing the gene expression of prepro-hypocretin.
- Prostaglandin D_2 is the most potent endogenous sleep-promoting substance, and the action mechanism of sleep induction is best characterized at neurologic and molecular levels.
- Overproduction of prostaglandin D_2 is associated with hypersomnia in patients with mastocytosis and African sleeping sickness or in mice after a pentylenetetrazole-induced seizure.
- Hypersomnia is also caused by cytokines produced during bacterial or viral infection and in various neurodegenerative diseases, and by intake of some sleep-promoting supplements.

CLINICAL DEFINITION OF HYPERSOMNIA

According to the International Classification of Sleep Disorders-3, central hypersomnia is classified into the following 6 categories: (1) Narcolepsy type 1 (previously narcolepsy with cataplexy); (2) Narcolepsy type 2 (previously narcolepsy without cataplexy); (3) Idiopathic hypersomnia; (4) Kleine-Levin syndrome; (5) Hypersomnia due to medical disorder, medication, or substance abuse; and (6) Insufficient sleep syndrome (**Box 1**). This classification is based on the clinical diagnosis based on polysomnography, multiple sleep latency tests, sleep diary, and so forth. The cause, diagnosis, and treatment of each of these sleep disorders are described in other sections of this issue. In this article, the author summarizes the neurobiology of hypersomnia from the molecular and biochemical points of view, mainly based on his research studies of hypocretin (Hcrt), prostaglandin (PG) D_2, and adenosine.

NARCOLEPSY AND THE HYPOCRETIN/OREXIN SYSTEM

Among the hypersomnias, narcolepsy has been the most well characterized in both clinical and basic research fields. Narcolepsy is diagnosed

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Box 1
Classification of hypersomnia according to the International Classification of Sleep Disorders-3

1. Narcolepsy type 1 (narcolepsy with cataplexy)
2. Narcolepsy type 2 (narcolepsy without cataplexy)
3. Idiopathic hypersomnia
4. Klein-Levin syndrome
5. Hypersomnia due to medical disorder, medication, or substance abuse
6. Insufficient sleep syndrome

by excessive daytime sleepiness, cataplexy, sleep-onset rapid eye movement sleep (SOREM), and sleep paralysis or hallucination,[1,2] and it is now known to be a disease caused by the degeneration of Hcrt-producing neurons.[3]

Discovered in 1998 by the research team of T. Kilduff at Stanford University, Hcrt was found to be a functionally unknown neuropeptide selectively expressed in the hypothalamus.[4] This group subsequently identified the gene encoding the prepropeptide of Hcrt, the biosynthetic pathway of isopeptide-1 and -2, and 2 subtypes of receptors for Hcrt, 1 and 2 (Fig. 1). These isopeptides were also independently isolated in 1998 as an orphan ligand for GPCR, HFGAN72, by T. Sakurai and M. Yanagisawa, University of Texas Southwestern, and termed orexins, because these researchers assumed that these peptides were involved in orexinergic regulation of feeding behavior.[5] Hcrt and orexin are the same peptide.

In 1999, the year following of the discovery of Hcrt and the identification of Hcrt receptors, the research team of E. Migno, Stanford University, showed that the Hcrt receptor gene is mutated in dogs with inherited canine narcolepsy,[6] the colony of which was established and maintained by Kilduff and Migno's mentor, Professor William C. Dement. The narcoleptic attack, involving SOREM and cataplexy-like behavior, was then reported to occur in the Hcrt/orexin gene knockout (KO) mice.[7] These 2 animal studies strongly suggested that abnormality of the Hcrt system causes human narcolepsy. In 2000, the research team of J.M. Siegel at University of California, Los Angeles, and of S. Nishino and E. Migno at Stanford University finally demonstrated that the Hcrt-producing neurons had disappeared in the hypothalamus of autopsied brain tissue from narcolepsy patients.[3,8,9] They measured the Hcrt content in the cerebrospinal fluid (CSF) of healthy volunteers and hypersomnia patients diagnosed as having narcolepsy or other neurodegenerative diseases and found that the Hcrt content was selectively and markedly decreased in those patients with narcolepsy, especially in most of the patients classified as having the cataplexy-associated type 1 narcolepsy.[10] Today, a decreased CSF level of Hcrt is used as an important marker for the diagnosis of narcolepsy. Epidemiologic studies

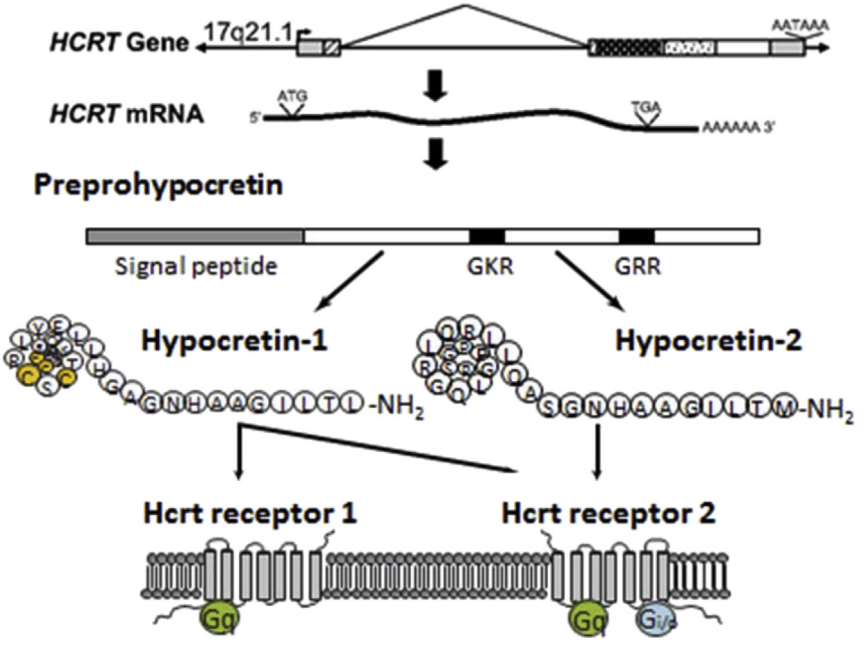

Fig. 1. Hcrt production and receptors.