Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 55 (Suppl 2) (2006) S36–S39
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Narcolepsy and the hypocretins

Richard J. Wurtman*

Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Abstract

Narcolepsy is a chronic neurologic disease characterized by excessive daytime sleepiness and one or more of three additional symptoms (cataplexy, or sudden loss of muscle tone; vivid hallucinations; and brief periods of total paralysis) related to the occurrence of rapid eye movement (REM) sleep at inappropriate times. The daytime sleepiness typically presents as a sudden overwhelming urge to sleep, followed by periods of sleep that last for seconds or minutes, or even longer. During daytime sleep episodes, patients may exhibit "automatic behavior," performing conventionalized functions (eg, taking notes), but not remembering having done so once they are awake. About 10% of narcoleptics are members of familial clusters; however, genetic factors alone are apparently insufficient to cause the disease, inasmuch as the most common genetic disorder, a mutation in chromosome 6 controlling the HLA antigen immune complex, although seen in 90% to 100% of patients, also occurs in as many as 50% of people without narcolepsy. A dog model of narcolepsy exhibits a mutation on chromosome 12 that disrupts the processing of the peptide neurotransmitter hypocretin. No such mutation characterizes human narcolepsy; however, cerebrospinal fluid (CSF) hypocretin levels are profoundly depressed in narcoleptic patients, and a specific reduction in hypocretin-containing neurons has been described. One hypothesis concerning the pathophysiology of narcolepsy proposes that the HLA subtype resulting from the mutation on chromosome 6 increases the susceptibility of hypocretin-containing brain neurons to immune attack. Because hypocretin may normally participate in the maintenance of wakefulness, the loss of neurons that release this peptide might allow REM sleep to occur at inappropriate times, ie, while the patient is awake, in contrast to its normal cyclic appearance after a period of slow-wave sleep. The cataplexy, hallucinations, and/or paralysis associated with REM episodes normally are unnoticed—or, at least, not remembered—when the transition to REM follows slow wave sleep, as is normally the case; however, they are remembered when, in people with narcolepsy, the REM episode starts during a period of wakefulness. The association of narcolepsy with a deficiency in a specific neurotransmitter, in this case, hypocretin, is reminiscent of the associations between Parkinson disease and dopamine, or early Alzheimer disease and acetylcholine.

1. Introduction

Narcolepsy is a chronic neurologic disease characterized by 4 sleep-related disturbances (although only about 10% of patients present with the full tetrad) [1-3]: *excessive daytime sleepiness*, sometimes described as "an insurmountable urge to sleep"; *total paralysis* at the beginning or end of sleep; and symptoms probably resulting from the onset of rapid eye movement (REM) sleep episodes during periods of wakefulness instead of, as is normally the case, during periods of slow wave sleep. These REM-related symptoms include, in 70% of patients [1], *cataplexy* (a sudden and brief loss of muscle tone, ranging from slurring of speech to a complete loss of posture, with full retention of consciousness), often triggered by intense emotions or even laughter. They also less commonly include vivid *hallucinations* during sleep onset or upon awakening. Daytime sleep episodes may be associated with "automatic behavior," in which the patient continues to perform conventionalized behaviors (eg, taking notes) but does not remember having done so once he or she awakens. Nocturnal sleep tends to be fragmented and is often described as not being restful, although the total number of hours spent sleeping each day is usually unaltered.

Narcolepsy afflicts perhaps 135 000 Americans [1], making it the third most common of the sleep disorders after sleep apnea and the restless legs syndrome. Symptoms first tend to appear at ages 10 to 25 years but have also been described in children as young as 3 years; they tend to worsen with time, sometimes decreasing in severity after age 60 years [1]. In most cases, the disease is sporadic; however, about 10% involve familial clusters [1]. Genetic factors alone are apparently insufficient to produce the disease, inasmuch as the most common genetic disturbance in persons with

* Tel.: +1 617 253 6731; fax: +1 617 253 6882.
E-mail address: dick@mit.edu.

0026-0495/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2006.07.011

narcolepsy [4,5]—a mutation on chromosome 6 affecting a human leukocyte antigen ([HLA] DR2/DQ6 [DQB1*0602]), seen in 90% to 100% of patients—is also found in 50% of nonnarcoleptic subjects. The diagnosis of narcolepsy is usually confirmed by finding abnormally timed REM episodes on polysomnographic recordings and by the Multiple Sleep Latency test. In that test, subjects are asked to try to fall asleep at several times during the day; normal individuals require, on average, 10 minutes to do so, whereas those with narcolepsy may fall asleep in less than 5 minutes. The treatment of narcolepsy, which often is less than fully satisfactory, involves administering a stimulant to diminish the daytime sleepiness and an antidepressant for the REM sleep–associated symptoms.

1.1. Symptomatic narcolepsy

Symptoms of narcolepsy can also occur in association with other neurologic diseases [4,6-8]. Nishino and Kanbayashi [4] have recently analyzed reports describing 116 such patients with "symptomatic narcolepsy," including 38 with inherited disorders (such as Niemann-Pick disease), 33 with brain tumors, 19 with a history of head trauma, 10 with multiple sclerosis, and 6 with vascular diseases. Such patients can exhibit the full constellation of symptoms seen in idiopathic narcolepsy, as well as the narcolepsy-associated reduction in cerebrospinal fluid (CSF) hypocretin levels described below; both the symptoms and the reduced CSF hypocretin tend to improve when the underlying neurologic disease is successfully treated.

2. Hypocretin in narcolepsy

In the few years since the discovery of the 2 hypocretin peptides in 1998 [9,10], considerable evidence, summarized below, has accumulated showing that brains of most narcoleptic patients are deficient in these compounds and that this deficiency may be related to the pathogenesis of the disease [3]. Narcolepsy thus becomes, along with Parkinson disease (dopamine) and early Alzheimer disease (acetylcholine), one of a very small number of syndromes in which symptoms clearly seem to arise in relation to one key neurotransmitter.

2.1. Biochemistry of hypocretin

The 2 neurotransmitter peptides, usually termed hypocretins, particularly by clinical investigators, were identified by 2 groups of investigators in 1998, based on use of a reverse pharmacology technique to identify ligands for G-protein–coupled receptors [9] and on identification of the novel prepropeptide formed by a messenger RNA extracted from rat hypothalamus [10]. The Sakurai et al [9] report also described 2 hypocretin receptors coupled to G proteins and the binding affinities of each for the 2 peptides, whereas the de Lecea et al [10] report showed that hypocretins are concentrated within synaptic vesicles and produce excitatory effects when applied to cultured hypothalamic cells.

Hypocretin-1 [10] was found to contain 33 amino acids, and hypocretin-B or hypocretin-2, 28 amino acids. Both peptides are derived from a common 130- to 131-amino-acid precursor, preprohypocretin [11]. Hypocretin-1 binds to both of the hypocretin receptors, OX1R and OX2R; through OX1R, it activates a Gq G protein, and through OX2R, both it and hypocretin-2 activate both Gq G and Gi/Go receptors. The ultimate effects of the hypocretins on postsynaptic neurons apparently involve decreasing potassium conductance [12,13]. Hypocretin receptors and the terminals of hypocretinergic neurons are abundant in rat hypothalamus, hippocampus, locus coeruleus, raphe nuclei, and cerebral cortex, among other brain regions [2,14].

Patch clamp recordings have shown that the neurotransmitters norepinephrine and serotonin tend to inhibit hypocretin-releasing neurons, whereas acetylcholine tends to be excitatory [15]. Moreover, the direct application of aminomethylphenylacetic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) agonists excite hypocretin neurons in mouse hypothalamus, whereas glutamate antagonists reduce their activity [16]. Administration of glucose or leptin also tends to inhibit these neurons, whereas ghrelin, a hormone whose plasma levels rise with fasting, is excitatory, raising the possibility that postprandial sleepiness results in part from diminished hypocretin release [2].

Although there is broad agreement that the hypocretins are somehow involved in the regulation of normal sleep and wakefulness, their exact functions in these processes remain unclear [17] and presently the subject of broad investigation (cf [17-20]). Hypocretin tends to be released within the brain at high levels during active waking and during REM sleep, and at minimal levels during non-REM sleep [20]. Its intracerebroventricular administration to conscious rats at the onset of the normal sleep period causes a dose-dependent increase in subsequent wakefulness (ie, during the second and third hours after dosing) associated with marked reductions in slow wave sleep and paradoxical sleep [21]. This was interpreted as reflecting a hypocretin-induced acceleration of locus coeruleus firing, a hypothesis consistent with the association in narcolepsy (described below) between low hypocretin levels and the inappropriate appearance of REM sleep episodes.

2.2. Initial evidence relating hypocretin to narcolepsy

One year after the hypocretins were discovered, Lin et al [22] identified a characteristic mutation in one of the hypocretins in 2 canine models of human narcolepsy, narcoleptic Doberman pinschers and Labrador retrievers, and proposed that the sleep disorders and cataplexy observed in these animals resulted from this mutation. A few weeks later, Chemelli et al [23] affirmed a relationship between the symptoms of narcolepsy and hypocretin deficiency by describing cataplexy-like states in hypocretin-deficient knockout mice. Then, in 2000, Nishino et al [24] reported major deficiencies in CSF hypocretin levels among most patients (subsequently shown to be 90% [25]) with narco-

lepsy, and 2 other laboratories described the virtual absence of hypocretin [26] and a major decrease in hypocretin-containing neurons [27] in brains of patients with narcolepsy.

In only a single patient studied to date [26] has the narcolepsy-related reduction in brain hypocretin been shown to result from mutations in the gene responsible for hypocretin production, as opposed to the loss of hypocretin-producing neurons [3]. Hence, the most widely accepted view concerning the mechanism of the hypocretin deficiency is that a degenerative process, probably immune in origin, selectively destroys hypocretin-releasing neurons, thereby producing the clinical syndrome of narcolepsy. If this hypothesis continues to be supported, it may lead to attempts to prevent or treat the disease immunologically. Moreover, narcolepsy will become one of a very few neurologic disorders—along with Parkinson disease, Alzheimer disease, amyotrophic lateral sclerosis, and, possibly, depression—to arise from the selective loss of a single population of neurons. In support of this hypothesis, recent studies suggest that the short-term administration of hypocretin-A can maintain wakefulness, suppress sleep, and inhibit attacks of cataplexy in mice made narcoleptic by the prior ablation of orexigenic neurons [23]. Studies that test hypocretin's actions and its roles in narcolepsy and normal sleep should be facilitated by the ongoing development of nonpeptidergic hypocretin antagonists that readily cross the blood-brain barrier [24-26,28-31].

3. Some future directions

The clear association between a deficiency in brain hypocretin levels and symptoms of narcolepsy places these peptides among a select group of neurotransmitters, along with nigrostriatal dopamine and hippocampal acetylcholine, deficiency of which can give rise to a brain disease (Parkinson and early Alzheimer disease). It also suggests possible ways of treating the narcolepsy (ie, with to-be-developed non-peptide hypocretin receptor agonists capable of crossing the blood-brain barrier) or of slowing progression of the disease with anti-immune drugs (if the loss of the hypocretin neurons is indeed caused by HLA antigen–related immune attack). The actual use of hypocretin agonists may be complicated if, eg, endogenous hypocretins suppress REM sleep onset episodically, and not continuously; it probably would not be desirable to suppress all REM sleep, including that which normally occurs within periods of slow wave sleep, so the agonists would have to be available only when the missing hypocretin neurons would normally be firing.

In addition, recognition of this association should facilitate the experimental analysis of sleep and wakefulness per se: It is generally believed that humans exhibit 3 main varieties of sleep-related behavior—wakefulness; slow wave sleep; and REM sleep—each of which reflects the activity of a network of brain neurons or "module." The transition from the "wakefulness module" into sleep is via the "slow wave sleep module," and transitions both into and out of the "REM sleep module" also are normally via slow wave sleep. Presumably, one or more neural switches determine whether slow wave sleep will continue, will segue into REM sleep, or will yield to wakefulness; however, no such switch allows a transition from wakefulness to REM sleep *unless* hypocretin is deficient. (Various hypnotic drugs, particularly the benzodiazepines, also affect the switching mechanisms, suppressing the transition from slow wave sleep into REM sleep.)

The putative "modules" underlying these 3 varieties of sleep-related behavior remain essentially "black boxes," and before the discovery of the hypocretin-narcolepsy relationship very little has been known about how the "switching" mechanisms operate. Careful analyses of the temporal patterns of wakefulness, slow wave sleep, and REM sleep among people or animal models with narcolepsy and among animals with selective neurosurgical or genetic lesions of hypocretin-secreting neurons should provide important insights into the mechanisms underlying switching. Hypocretins apparently are involved in other cyclic regulatory processes besides sleep-wakefulness, eg, those affecting metabolism and food consumption. When hypocretin-releasing brain neurons are activated (during wakefulness) and release their neurotransmitter to suppress REM onset, is this activation cyclic, and is hypocretin release from one set of neurons (eg, those terminating in the locus coeruleus) paralleled by that in brain areas less associated with behavioral activation and more with metabolism (eg, the hypothalamus)? Or are different sets of hypocretin neurons differentially controlled? It can be anticipated that the next few years will see major advances in our understanding of the basic biology of these neurons and, through this understanding, of sleep-wakefulness in general.

Acknowledgments

This article was supported in part by grants from the National Institute of Mental Health and the Center for Brain Sciences and Metabolism Charitable Trust.

References

[1] Narcolepsy fact sheet, National Institute of Neurological Disorders and Stroke. http://www.ninds.nih.gov/disorders.
[2] Sakurai T. Physiological reviews: roles of hypocretin/hypocretin in regulation of sleep/wakefulness and energy homeostasis. Sleep Med Rev 2005;9:231-42.
[3] Kilduff TS. Hypocretin/hypocretin: maintenance of wakefulness and a multiplicity of other roles. Sleep Med Rev 2005;9:227-30.
[4] Nishino S, Kanbayashi T. Symptomatic narcolepsy, cataplexy, and hypersomnia, and their implications in the hypothalamic hypocretin/hypocretin system. Sleep Med Rev 2005;9:269-310.
[5] Mignot E, Lammers G, Ripley B. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 2002;59:1553-62.
[6] Bonduelle M, Degos C. Symptomatic narcolepsies: a critical study. In: Gulleminault C, Dement W, Passouant P, editors. Narcolepsy. New York: Spectrum; 1976. p. 313-32.

[7] Autret A, Lucas B, Henry-Lebras F, et al. Symptomatic narcolepsies. Sleep 1994;17(8 Suppl):S21-S24.
[8] Aldrich M, Naylor M. Narcolepsy associated with lesions of the diencephalon. Neurology 1989;39:1505-8.
[9] Sakurai T, Amemiya A, Ishii M, et al. Hypocretins and hypocretin receptors: a family of hypothalamic neuropeptides and G protein–coupled receptors that regulate feeding behaviour. Cell 1998;92: 573-85.
[10] de Lecea L, Kilduff TS, Peyron C, et al. The hypocretin: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci U S A 1998;95:322-7.
[11] Sakurai T, Moriguchi T, Furuya K, et al. Structure and function of human prepro-hypocretin gene. J Biol Chem 1999;274:17771-6.
[12] Yang B, Sampson K, Ferguson AV. Excitatory effects of hypocretin-A on nucleus tractus solitarius neurons are mediated by phospholipase C and protein kinase C. J Neurosci 2003;23:6215-22.
[13] Ivanov A, Aston-Jones G. Hypocretin/orexin depolarizes and decreases potassium conductance in locus coeruleus neurons. Neuroreport 2000;11:1755-8.
[14] Marcus JN, Ashkenasi CJ, Lee CE, et al. Differential expression of hypocretin receptors 1 and 2 in the rat brain. J Comp Neurol 2001;435:6-25.
[15] Yamanaka A, Muraki Y, Tsujino N, et al. Regulation of hypocretin neurons by the monoaminergic and cholinergic systems. Biochem Biophys Res Commun 2003;303:120-9.
[16] Li Y, Gao XB, Sakurai T. Hypocretin/orexin excites hypocretin neurons via a local glutamate neuron—a potential mechanism for orchestrating the hypothalamic arousal system. Neuron 2002;36:1169-81.
[17] Baumann CR, Bassetts CL. Hypocretins (orexins) and sleep-wake disorders. Lancet 2005;10:673-82.
[18] Saper CB, Cano G, Scammell TE. Homeostatic, circadian, and emotional regulation of sleep. J Comp Neurol 2005;493:92-8.
[19] Mignot E. Sleep, sleep disorders and hypocretin. Sleep Med 2004;(Suppl 1):S2-S8.
[20] Siegel JM. Hypocretin (orexin): role in normal behavior and neuropathology. Annu Rev Psychol 2004;55:125-48.
[21] Piper DC, Upton N, Smith MI, Hunter AJ. The novel brain neuropeptide, orexin-A, modulates the sleep-wake cycle of rats. Eur J Neurosci 2000;12:726-30.
[22] Lin L, Faraco J, Kadotani H, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (hypocretin) receptor 2 gene. Cell 1999;98:365-76.
[23] Chemelli RM, Willie JT, Sinton CM, et al. Narcolepsy in hypocretin knockout mice: molecular genetics of sleep regulation. Cell 1999;98:437-51.
[24] Nishino S, Ripley B, Overeem S, et al. Hypocretin (hypocretin) deficiency in human narcolepsy. Lancet 2000;355:39-40.
[25] Baumann CR, Bassetti CL. Hypocretins (orexins): clinical impact of the discovery of neurotransmitter. Sleep Med Rev 2005;9: 253-68.
[26] Peyron C, Faraco J, Rogers W, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med 2000;9:991-7.
[27] Thannickal TC, Moore RY, Nienhuis R, et al. Reduced number of hypocretin peptides in human narcolepsy. Neuron 2000;27: 469-74.
[28] Mieda M, Wille JT, Hara J, et al. Orexin peptides prevent cataplexy and improve wakefulness in an orexin neuron-ablated model of narcolepsy in mice. Proc Natl Acad Sci U S A 2004;101:4649-954.
[29] Samson WK, Taylor MM, Ferguson AV. Non-sleep effects of hypocretin/orexin. Sleep Med Rev 2005;9:243-52.
[30] Rodgers RJ, Halford JC, Nunes de Souza RL, et al. SB-334867, a selective hypocretin-1 receptor antagonist, enhances behavioral satiety and blocks the hyperphagic effect of hypocretin-A in rats. Eur J Neurosci 2001;13:1444-52.
[31] Hirose M, Egashira S, Goto YN, et al. *N*-Acyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline: the first hypocretin-2 receptor selective non-peptidic antagonist. Bioorg Med Chem Lett 2003;13:4497-9.