NARCOLEPSY RESEARCH: PAST, PRESENT, AND FUTURE PERSPECTIVES

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INTRODUCTION

In 1877, Westphal described a patient with hypersomnia and episodic muscle weakness. He did not feel that these weakness attacks could simply be explained by "epileptoid" phenomenon (43). The next year, Fischer described a similar case (9). By 1880, Gélineau decided that patients with these symptoms represented a distinct clinical entity and he called it "narcolepsy" (11). In 1902, Loewenfeld noted the importance of cataplexy in this disorder (21), and in 1934 Daniels published an important review on the topic which helped to galvanize interest in further study (6). In 1957, Yoss and Daly discussed the "clinical tetrad" which included hypersomnia, cataplexy, hypnagogic hallucinations, and sleep paralysis (45). In 1960, Vogel noted that patients with narcolepsy had early onset of REM sleep on their electroencephalograms (42). At the First International Symposium on Narcolepsy in 1975, the symptom of disturbed nocturnal sleep was added to the clinical diagnostic criteria for narcolepsy (12). For many years the etiology and mechanisms of this disease were poorly understood. It was not until the early 1970s when the exciting animal and human research first started to unravel the mysteries of the genetics and physiology of narcolepsy. This research will be discussed below.

THE CLINICAL SYNDROME

Narcolepsy is a disorder in which the ability to regulate sleep-wake states does not function properly. Patients with narcolepsy typically have daytime somnolence, cataplexy, sleep paralysis, hypnagogic hallucinations, and poor nocturnal sleep. With the exception of cataplexy, all of these symptoms can be seen in other disorders with excessive daytime sleepiness, and can even be considered an occasional part of normal human experience. Hypnagogic hallucinations are vivid, realistic visual, auditory, or tactile dreamlike sensations that occur upon falling asleep (they are called hypnopompic if they occur upon awakening). These hallucinations are often so realistic that the patient will take action when they feel that they are threatened for example calling the police when they think there is an intruder in the house. Sleep paralysis is the onset of immobilization before a patient has actually fallen asleep, or

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the persistence of paralysis after the patient has awoken. It is similar to cataplexy, but there is no trigger and it only occurs upon attempts to fall asleep or upon awakening. It is sometimes found in combination with threatening hypnagogic hallucinations, so that the patient describes being "scared stiff." Nocturnal sleep is characterized by poorly organized sleep architecture subjectively and using polysomnography. All of these symptoms can be conceptualized as representing a dysfunction of sleep-wake state regulation. For example, hypnagogic hallucinations are believed to represent the onset of dreaming (REM sleep) while the patient is still awake, and sleep paralysis - the onset of REM paralysis on the wake state.

The symptom of cataplexy is unique to narcolepsy. It is thought to represent the paralysis of REM sleep intruding onto wakefulness (35) but is also uniquely regulated. This is the most dramatic example of the improper sleep state regulation found in narcolepsy. It is defined as the sudden loss of muscle tone associated with emotionally charged thoughts or activities. The trigger is usually humor or anger. In its most subtle form it can present as mild relaxation of facial features, slurred speech, or sagging jaw. In its extreme form it can lead to complete collapse, however it does not typically involve a change in the level of consciousness. It usually lasts for a few seconds to minutes. Cataplexy is specific for narcolepsy, but its prevalence ranges between 60% to 100% of narcoleptic patients, depending on the clinical criteria used to diagnose narcolepsy (2). This has lead to the proposal that the diagnosis of narcolepsy be divided into two categories: narcolepsy with and without cataplexy. This hypothesis has been further substantiated by the observation that hypocretin deficiency is mostly in cases with cataplexy (26).

Treatment consists of a combination of behavioral and pharmaceutical methods. Patients are usually refreshed by short naps and are encouraged to discuss scheduled naps with their employers. They should also consider occupations that are mentally and physically stimulating rather than ones that are sedentary. Three categories of medication are used to treat narcolepsy: Central Nervous System (CNS) activating agents, anti-cataplectic agents, and medications that consolidate nighttime sleep. Until the 1990s amphetamines were the primary drugs used for CNS activation, but a newer drug, modafinil, was developed and is thought to be safer (4, 10). It is now considered by many clinicians to be first-line treatment for the excessive daytime sleepiness associated with narcolepsy. Antidepressants have been long used for cataplexy. The selective serotonin and adrenergic reuptake inhibitors seem to treat cataplexy and have less side-effects than the tricyclic antidepressants (16). The newest narcolepsy medication is gamma-hydroxybutyrate. It is unique in that, not only does it help with consolidation of nighttime sleep, but it also seems to improve daytime sleepiness and cataplexy (19, 37, 41).

Although narcolepsy-cataplexy is usually sporadic in it appearance, it has long been thought to have a genetic component. The prevalence is 0.02%-0.18% in the general population, across ethnic groups (23). In first degree relatives, the risk is 10-40 times that of the general population, but there is a high discordance between monozygotic twins (23). Thus, a combination of familial and environmental factors contributes to the development of narcolepsy. The finding that hypocretin (orexin)

is involved in human narcolepsy has lead to a better understanding of the physiologic and genetic underpinnings of this disease. This finding was the culmination of a long lasting collaboration between animal and human researchers.

ANIMAL STUDIES

The discovery of canine narcolepsy was a landmark in narcolepsy research. Until that time, there was not an animal model for narcolepsy. It was first reported in a dachshund by Knecht (18) and then in a poodle by Mitler (29). Over the next few years, a worldwide search was begun, to find more dogs with narcolepsy. Although a number of other breeds were discovered in the following years, and attempts were made to breed them, it was not until 1979 when the breeding of Dobermans led to the first genetic transmission (1). In the late 1980s, the first informative crosses occurred, which confirmed the recessive nature of the trait. Subsequently, the trait was determined to be transmitted as a single autosomal recessive gene with full penetrance. This gene was designated canarc-1 (28). In 1989, linkage analysis and marker screening were initiated. By 1991, a probe for the human switch region of the mu-immunoglobulin heavy-chain gene identified a tight linkage marker for canarc-1 (28).

Chromosome walking was difficult at that time, given the lack of available genomic libraries, so a canine genomic bacterial chromosome artificial (BAC) library was developed. In the late 1990s, using fluorescence in situ hybridization and the newly developed BAC library, the linkage marker was located on canine chromosome 12 (20). Next, using a combination of chromosome walking and microsatellite markers, the candidate area was narrowed down to a small segment on chromosome 12 (20). This segment only included two known genes, and one of these was the hypocretin receptor 2 gene (Hcrtr2) (20). On sequencing this segment from the chromosomes of narcoleptic dogs, a mutation was found in the canine Hcrtr2 gene of narcoleptic Dobermans(20). Subsequently, two more narcolepsy-causing mutations were found in the canine Hcrtr2 gene of two other breeds with a genetic form of the disorder (17). Within weeks of this landmark discovery, a pre-prohypocretin knockout mouse was found to have symptoms consistent with narcolepsy (5).

In 1998, the year prior to the discovery of the Hcrtr2 mutation in dogs, hypocretin (Hcrt) 1 and 2, as well as their receptors (Hcrtr1 and Hcrtr2), were identified in rat brains (7, 36). The Hcrt peptides were almost exclusively located in neurons of the dorsolateral hypothalamus (7, 36). These neurons projected to diffuse areas of the brain including cortex, basal forebrain, thalamus, central gray, and locus coeruleus. Because these peptides appeared to be located in synaptic vesicles, and the application of Hcrt2 to hypothalamic neuron cultures produced neuroexcitation, hypocretins were hypothesized to be neurotransmitters (7, 36). Given their hypothalamic location, hypocretins were assumed to be involved in the regulation of feeding and/or energy balance (7, 36). Later studies on the widespread distribution

of the neuronal projections suggested that hypocretins might also be involved in other complex functions including blood pressure regulation, neuroendocrine regulation, thermoregulation, and the maintenance of a waking state (34).

Recent reports have further implicated hypocretins in the sleep-wake system and narcolepsy. It was recently demonstrated that intracerebroventricular (ICV) administration of Hcrt1 to control dogs showed a dose dependent increase in wakefulness and a decrease in slow-wave sleep and in REM sleep, whereas ICV administration of Hcrt1 to narcoleptic dogs did not affect sleep or cataplexy (30). It was also shown that hypocretin increased firing in the locus coeruleus as well as decreased REM sleep and increased wakefulness in rats (15). Another experiment, in squirrel monkeys, showed a partial circadian cycle in CSF hypocretin-1 levels that was thought to be evidence of wake regulation (46). Another recent study showed that both Hcrt and Hcrtr2 deficient mice have disrupted wakefulness, but only the Hcrt deficient mice have severe cataplexy (44). Taken together, these findings support the hypothesis that hypocretins are necessary for the regulation of wakefulness.

The relationship that hypocretins have with other sleep-associated neurotransmitters provides further evidence for their role in the regulation of wakefulness, the most notable example being histamine. In particular, the excitatory projections of hypocretin neurons are dense to the tuberomammillary nucleus (TMN) which is primarily histaminergic (22). Histamine has been implicated in the control of wakefulness via the sedating effects of antihistamines, microdialysis studies of histamine levels in cat brains, and various knockout mice experiments (8, 32, 38). Given the anatomic relationship between hypocretin neurons and the histaminergic system, it has been hypothesized that the wake regulating effects of hypocretins are mediated by histamine (3, 39). This is probably an oversimplification, as it does not take into account the feedback mechanisms between hypocretins, histamine, and the other monoaminergic systems.

HUMAN STUDIES

In a sense, the discovery of a genetic substrate for animal narcolepsy was the end of a long search for the cause of narcolepsy in animals. But this information was only one component that contributed to the understanding of the complex syndrome of human narcolepsy. Shortly after the first genetic transmission occurred in dogs, Drs. Honda, Asaka, and Juji began to search for genetic markers in humans (13). Initially, patients were found to have an increased frequency of the HLA-DR2 allele (14). However, it became apparent that in Black patients with narcolepsy, HLA-DR2 was not as strong a marker as it was in Caucasians and Japanese (27). Later studies revealed that DQB1*0602 was a much better marker across all ethnic groups (27). Unfortunately, it is an imperfect marker for two reasons: 1) there have been reports of patients with narcolepsy-cataplexy who are DQB1*0602 negative (25), and 2) the baseline frequency in the general population is as high as 38%, which makes it less specific (24).

With the discovery of hypocretin abnormalities in animal models of narcolepsy, the obvious next step was to check for these abnormalities in humans. In 2000, patients with narcolepsy were found to have very low levels of cerebrospinal fluid hypocretin levels, compared to controls (31). It has since been reported that low hypocretin levels can be found in a handful of neurologic disorders, but in general it is very specific for narcolepsy-cataplexy (26). Also, mutation screening for Hcrt, Hcrtr1, and Hcrtr2 did not reveal hypocretin mutation in humans, except for a single patient with a mutation in the Hcrt signal peptide (33). Neuropathologic studies have shown an absence of hypocretin neurons in the hypothalami of narcoleptic subjects, but no clear evidence of damage to these areas (33, 40). This information, combined with the HLA association, has lead to the hypothesis that narcolepsy is caused by an autoimmune attack on the hypocretin producing cells in the hypothalamus.

FUTURE DIRECTIONS

Since all of these groundbreaking discoveries have occurred just within the last four years, there are many future directions for narcolepsy research. First, the test for CSF hypocretin may begin to play an integral role in the diagnosis of narcolepsy (26). It is already being used in research patients, and recent articles have discussed its proper role in the diagnosis of patients with narcolepsy (26). There is also the possibility that a serum test for hypocretin will be developed, although this still needs to be proven as a feasible option. Second, the autoimmune basis for narcolepsy has yet to be proven, and its trigger is still unknown. Third, the possibility of using a hypocretin agonist as a treatment for narcolepsy will need to be investigated. Fourth, long-term therapies such as gene therapy or cell transplantation to repair or replace the hypocretin neurons will need to be examined. Finally, it is still unclear as to the physiologic role of hypocretins in normal individuals. Although, we have a strong suspicion that they are involved in wake regulation and possibly feeding/energy balance, we have yet to clearly define their role as a neuropeptide.

DISCUSSION

Narcolepsy is a disorder of hypersomnia that is thought to be secondary to poor regulation of sleep-wake states. Cataplexy is a unique symptom of narcolepsy that provides a good example of this dysfunction of sleep-wake state regulation. Although it was described as early as 1877, any understanding of its mechanisms did not occur until the first animal model was described in the 1970s. Over the last thirty years, the genetic and physiologic basis for narcolepsy has been gradually uncovered. With the discovery of deficient hypocretin in human narcoleptics, a new phase in the understanding of the mechanisms, causes, and treatments for narcolepsy has begun. This knowledge should lead to many discoveries that will eventually change the way we think about and treat narcolepsy.

REFERENCES

1. BAKER, T.L., FOUTZ, A.S., MCNERNEY, V., MITLER, M.M., AND DEMENT, W.C. Canine model of narcolepsy: genetic and developmental determinants. *Exp. Neurol.*, **75:** 729-742, 1982.

2. BASSETTI C. AND ALDRICH M.S. Narcolepsy. *Neurol. Clin.*, **14:** 545-571, 1996.

3. BEUCKMANN, C.T. AND YANAGISAWA, M. Orexins: from neuropeptides to energy homeostasis and sleep/wake regulation. *J. Mol. Med.*, **80:** 329-342, 2002.

4. BROUGHTON, R.J., FLEMING, J.A., GEORGE, C.F., HILL, J.D., KRYGER, M.H, MOLDOFSKY, H., MONTPLAISIR, J.Y., MOREHOUSE, R.L, MOSCOVITCH, A., AND MURPHY, W.F. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology*, **49:** 444-451, 1997.

5. CHEMELLI, R.M., WILLIE, J.T., SINTON, C.M., ELMQUIST, J.K., SCAMMELL, T., LEE, C., RICHARDSON, J.A., WILLIAMS, S.C., XIONG, Y., KISANUKI, Y., FITCH, T.E., NAKAZATO, M., HAMMER, R.E., SAPER, C.B. AND YANAGISAWA, M. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell*, **98:** 437-451, 1999.

6. DANIELS, L.E. Narcolepsy. *Medicine*, **13:** 1-122, 1934.

7. DE LECEA, L., KILDUFF, T.S., PEYRON, C., GAO, X.-B., FOYE, P.E., DANIELSON, P.E., FUKUHARA, C., BATTENBERG, E.L.F., GAUTVIK, V.T., BARTLETT, F.S., FRANKEL, W.N., VAN DEN POL, A.N., BLOOM, F.E., GAUTVIK, K.M. AND SUTCLIFFE, J.G. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc. Natl. Acad. Sci. USA*, **95:** 322-327, 1998.

8. DUGOVIC, C., KOEHL, M., RONTAL, A.D., TOYOTA, H., LOVENBERG, T.W., AND TUREK, F.W. Sleep in mice lacking the histamine H3 receptor, a putative genetic animal model for REM sleep behavior disorder. *Sleep*, (suppl.) **25:** A114-A115, 2002.

9. FISCHER, F. Epileptoide schlafzustände. *Arch. F. Psychiat.*, **8:** 200-203, 1878.

10. FRY, J.M. Treatment modalities for narcolepsy. *Neurology*, (suppl. 1) **50:** S43-S48, 1998.

11. GÉLINEAU, J. De la narcolepsie. *Gaz. d. hôp.*, **53:** 626-628, 1880.

12. GUILLEMINAULT, C., DEMENT, W.C., AND PASSOUANT, P. *Narcolepsy*. New York, NY: Spectrum Publications, 1975.

13. HONDA, Y., ASAKE, A., TANAKA, Y., AND JUJI, T. Discrimination of narcolepsy by using genetic markers and HLA. *Sleep Res.*, **1:** 254, 1983.

14. HONDA, Y., DOI, Y., JUJI, T., AND SATAKE, M. Narcolepsy and HLA: positive DR2 as a prerequisite for the development of narcolepsy. *Folia. Psychiatr. Neurol. Jpn.*, **38:** 360, 1984.

15. HORVATH, T.L., PEYRON, C., DIANO, S., IVANOV, A., ASTON-JONES, G., KILDUFF, T.S., AND VAN DEN POL, A.N. Hypocretin (orexin) activation and synaptic innervation of the locus coeruleus noradrenergic system. *J. Comp. Neurol.*, **415:** 145-159, 1999.

16. HUBLIN, C. Narcolepsy: current drug treatment options. *CNS Drugs*, **6:** 426-436, 1996.

17. HUNGS, M., FAN, J., LIN, L., LIN, X., MAKI, R.A., AND MIGNOT E. Identification and functional analysis of mutations in the hypocretin (orexin) genes of narcoleptic canines. *Genome Res.*, **11:** 531-539, 2001.

18. KNECHT, C.D., OLIVER, J.E., REDDING, R., SELCER, R. AND JOHNSON, G. Narcolepsy in a dog and a cat. *J. Am. Vet. Med. Assoc.*, **162:** 1052-3, 1973.

19. LAMMERS, G.J., ARENDS, J., DECLERCK, A.C., FERRARI, M.D., SCHOUWINK, G., AND TROOST, J. Gamma-hydroxybutyrate and narcolepsy: a double-blind placebo-controlled study. *Sleep*, **16:** 216-220, 1993.

20. LIN, L., FARACO, J., LI, R., KADOTANI, H., ROGERS, W., LIN, X., QIU, X., DE JONG, P.J., NISHINO, S. AND MIGNOT, E. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell*, **98:** 365-76, 1999.

21. LOEWENFELD, L. Ueber narkolepsie. *München. med. Wchnschr.*, **49:** 1041-1045, 1902.

22. MARCUS, J.N., ASCHKENASI, C.J., LEE, C.E., CHEMELLI, R.M., SAPER, C.B., YANAGISAWA, M., AND ELMQUIST, J.K. Differential expression of orexin receptors 1 and 2 in the rat brain. *J. Comp. Neurol.*, **435:** 6-25, 2001.

23. MIGNOT, E. Genetic and family aspects of narcolepsy. *Neurology*, (suppl 1) **50:** S16-S22, 1998.

24. MIGNOT, E., HAYDUK, R., BLACK, J., GRUMET, F.C., AND GUILLEMINAULT, C. HLA DQB1*0602 is associated with cataplexy in 509 narcoleptic patients. *Sleep*, **20:** 1012-1020, 1997.

25. MIGNOT, E., KIMURA, A., LATTERMANN, A., LIN, X., YASUNAGA, S., MUELLER-ECKHARDT, G., RATTAZZI, C., LIN, L., GUILLEMINAULT, C., GRUMET, F.C., MAYER, G., DEMENT, W.C., AND UNDERHILL, P. Extensive HLA class II studies in 58 non-DRB1*15 (DR2) narcoleptic patients with cataplexy. *Tissue Antigens*, **49:** 329-341, 1997.

26. MIGNOT, E., LAMMERS, G.J., RIPLEY, B., OKUN, M., NEVSIMALOVA, S., OVEREEM, S., VANKOVA, J., BLACK, J., HARSH, J., BASSETTI, C., SCHRADER, H., AND NISHINO, S. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch. Neurol.*, **59:** 1553-1562, 2002.

27. MIGNOT, E., LIN, X., ARRIGONI, J., MACAUBAS, C., OLIVE, F., HALLMAYER, J., UNDERHILL, P., GUILLEMINAULT, C., DEMENT, W.C. AND GRUMET, F.C. DQB1*0602 and DQA1*0102 (DQ1) are better markers than DR2 for narcolepsy in caucasian and black americans. *Sleep*, **17:** S60-S67, 1994.

28. MIGNOT, E., WANG, C., RATTAZZI, C., GAISER, C., LOVETT, M., GUILLEMINAULT, C., DEMENT, W.C., AND GRUMET, F.C. Genetic linkage of autosomal recessive canine narcolepsy with a μ immunoglobulin heavy-chain switch-like segment. *Proc. Natl. Acad. Sci. USA*, **88:** 3475-3478, 1991.

29. MITLER, M.M., BOYSEN, B.G., CAMPBELL, L. AND DEMENT, W.C. Narcolepsy-cataplexy in a female dog. *Exp. Neurol.*, **45:** 332-40, 1974.

30. NISHINO, S., FUJIKI, N., YOSHIDA, Y., AND MIGNOT, E. The effects of hypocretin-1 (orexin a) in hypocretin receptor 2 gene mutated and hypocretin ligand-deficient narcoleptic dogs. *Sleep*, (abstract supplement) **26:** A287, 2003.

31. NISHINO, S., RIPLEY, B., OVEREEM, S., LAMMERS, G.J., AND MIGNOT, E. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet*, **355:** 39-40, 2000.

32. PARMENTIER, R., OHTSU, H., DJEBBARA-HANNAS, Z., VALATX, J.L., WATANABE, T., AND LIN, J.S. Anatomical, physiological, and pharmacological characteristics of histidine decarboxylase knock-out mice: evidence for the role of brain histamine in behavioral and sleep-wake control. *J. Neurosci.*, **22:** 7695-7711, 2002.

33. PEYRON, C., FARACO, J., ROGERS, W., RIPLEY, B., OVEREEM, S., CHARNAY, Y., NEVSIMALOVA, S., ALDRICH, M., REYNOLDS, D., ALBIN, R., LI, R., HUNGS, M., PEDRAZZOLI, M., PADIGARU, M., KUCHERLAPATI, M., FAN, J., MAKI, R., LAMMERS, G.J., BOURAS, C., KUCHERLAPATI, R., NISHINO, S., AND MIGNOT, E. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat. Med.*, **6:** 991-997, 2000.

34. PEYRON, C., TIGHE, D.K., VAN DEN POL, A.N., DE LECEA, L., HELLER, H.C., SUTCLIFFE, J.G., AND KILDUFF, T.S. Neurons containing hypocretin (orexin) project to multiple neuronal systems. *J. Neurosci.*, **18:** 9996-10015, 1998.

35. RECHTSCHAFFEN A. AND DEMENT W.C. Studies on the relation of narcolepsy, cataplexy, and sleep with low voltage random EEG activity. *Res. Publ. Assoc. Res. Nerv. Ment. Dis.*, **45:** 488-505, 1967.

36. SAKURAI, T., AMEMIYA, A., ISHII, M., MATSUZAKI, I., CHEMELLI, R.M., TANAKA, H., WILLIAMS, S.C., RICHARDSON, J.A., KOZLOWSKI, G.P., WILSON, S., ARCH, J.R.,

BUCKINGHAM, R.E., HAYNES, A.C., CARR, S.A., ANNAN, R.S., MCNULTY, D.E., LIU, W.S., TERRETT, J.A., ELSHOURBAGY, N.A., BERGSMA, D.J., AND YANAGISAWA, M. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*, **92**: 573-585, 1998.

37. SCRIMA, L., HARTMAN, P.G., JOHNSON, F.H., THOMAS, E.E., AND HILLER, F.C. The effects of gamma-hydroxybutyrate on the sleep of narcolepsy patients: a double-blind study. *Sleep*, **13**: 479-490, 1990.

38. STRECKER, R.E., NALWALK, J., DAUPHIN, L. J., THAKKAR, M.M., CHEN, Y., RAMESH, V., HOUGH, L.B., AND MCCARLEY, R.W. Extracellular histamine levels in the feline preoptic/anterior hypothalamic area during natural sleep-wakefulness and prolonged wakefulness: an in vivo microdialysis study. *Neuroscience*, **113**: 663-670, 2002.

39. TAHERI, S., ZEITZER, J.M., AND MIGNOT, E. The role of hypocretins (orexins) in sleep regulation and narcolepsy. *Ann. Rev. Neurosci.*, **25**: 283-313, 2002.

40. THANNICKAL, T.C., MOORE, R.Y., NIENHUIS, R., RAMANATHAN, L., GULYANI, S., ALDRICH, M., CORNFORD, M., AND SIEGEL, J.M. Reduced number of hypocretin neurons in human narcolepsy. *Neuron*, **27**: 469-474, 2000.

41. US XYREM MULTICENTER STUDY GROUP. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. *Sleep*, **25**: 42-49, 2002.

42. VOGEL, G. Studies in psychophysiology of dreams. III. The dream of narcolepsy. *Arch. Gen. Psychiatry*, **3**: 421-428, 1960.

43. WESTPHAL, C. Eigenthümliche mit einschlafen verbundene anfälle. *Arch. f. Psychiat.*, **7**: 631-635, 1877.

44. WILLIE, J.T., CHEMELLI, R.M., SINTON, C.M., TOKITA, S., WILLIAMS, S.C., KISANUKI, Y.Y., MARCUS, J.N., LEE, C., ELMQUIST, J.K., KOHLMEIER, K.A., LEONARD, C.S., RICHARDSON, J.A., HAMMER, R.E., AND YANAGISAWA, M. Distinct narcolepsy syndromes in orexin receptor-2 and orexin null mice: molecular genetic dissection of non-rem and rem sleep regulatory processes. *Neuron*, **38**: 715-730, 2003.

45. YOSS, R.E. AND DALY, D.D. Criteria for the diagnosis of the narcoleptic syndrome. *Proc. Staff Meet. Mayo Clin.*, **32**: 320-328, 1957.

46. ZEITZER, J.M., BUCKMASTER, C.L, PARKER, K.J., HAUCK, C.M., LYONS, D.M. AND MIGNOT, E. Circadian and homeostatic regulation of hypocretin in a primate model: implications for the consolidation of wakefulness. *J. Neurosci.*, **23**: 3555-3560, 2003.