HIGHLIGHTS

SLEEP

A nap hand for narcolepsy

With more than 40 million adult Americans suffering from sleep problems, the search for preventative or curative treatment strategies is an important goal for both academic and clinical researchers. This goal moved a step closer with the publication of a paper in *Nature Medicine* that investigated the role of hypocretins in human narcolepsy.

Narcolepsy is a disabling sleep disorder characterized by excessive sleepiness during the normal waking hours that can involve cataplexy (loss of skeletal muscle tone without loss of consciousness), sleep paralysis (inability to move when falling asleep or awakening) and hypnagogic hallucinations (dream-like states). The recently discovered hypocretin peptides (also known as orexins) are neurotransmitters that have been localized to a population of cells within the hypothalamus with projections to other areas of the brain. Animal studies indicate that enhanced hypocretin systems promote wakefulness and that disruption of this system can lead to narcolepsy. Peyron and colleagues explored the role of hypocretins in human narcolepsy using two complementary approaches: mutation screening of three hypocretin loci, the precursor preprohypocretin (*Hcrt*) and two hypocretin receptors (*Hcrtr 1* and *Hcrtr 2*), and neuropathological analysis.

The mutation screen of 74 patients with a family history of narcolepsy, or who carry a specific human leukocyte antigen that has been linked to a predisposition to narcolepsy, revealed only one severe, early-onset case of narcolepsy associated with the predicted dominant mutation in the *Hcrt* locus. Interestingly, the severity and early presentation of this particular case was more similar to genetically induced narcolepsy in animals than most cases of human narcolepsy which typically arise during adolescence. The authors concluded that hypocretin genes are not usually involved in predisposition to human narcolepsy.

However, pathological results did show a link between hypocretin and narcolepsy — *in situ* hybridization studies showed an absence of hypocretin transcripts in the hypothalamus of all patients examined. Moreover, hypocretin peptide was undetectable in projection areas in the cortex and pons, supporting earlier data showing its absence in the cerebrospinal fluid of narcoleptic patients. These exciting findings support a role for hypocretin peptides in sleep disorders such as narcolepsy and suggest new therapeutic strategies for the treatment of this disabling condition.

Peter Collins

References and links

ORIGINAL RESEARCH PAPER Peyron, *et al.* A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nature Med.* **6**, 991–997 (2000)

FURTHER READING Nishino, S. *et al.* Hypocretin (orexin) deficiency in human narcolepsy. *Lancet* **355**, 39–40 (2000). | Siegel, J. M. Narcolepsy: A key role for hypocretins. *Cell* **98**, 409–412 (2000)

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