ELSEVIER

Sleep Medicine 1 (2000) 147–148

SLEEP MEDICINE

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Journal search and commentary

Article reviewed: Hypocretin (orexin) deficiency in human narcolepsy ☆

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Category

Narcolepsy, genetics, neurochemistry

Objectives

To compare CSF levels of hypocretin of patients with narcolepsy to those of normal controls.

Study design

Between subject comparison

Study population

Nine patients with narcolepsy with cataplexy and eight controls without narcolepsy (average ages ± SD 48.6 ± 14.4 and 40.3 ± 13.3 years; male:female 5:4 and 3:5, respectively).

Methods

The clinical history of controls and patients were evaluated by an experienced clinician. The diagnosis of narcolepsy required, in addition to sleepiness, the presence of cataplexy. All narcolepsy patients had a standard MSLT with average sleep latency of 5 min or less and with at least one sleep-onset REM episode. CSF samples were obtained from a lumbar puncture performed between 9:30 AM and 3:45 PM. Blinded analyses of 1 cc of CSF used the Jodine-125 hypocretin-l radioimmunoassy. All values were measured twice.

Results

Hypocretin-1 values for the normals showed little variation and ranged from 250 to 285 pg/ml. Seven of the nine narcoleptic patients had hypocretin levels so low they were undetectable (<40 pg/ml), while one other had an essentially normal value at 255 pg/ml and one had an abnormally high value at 638 pg/ml. There were no indications for effects from time of day of lumbar puncture (for controls), prior medication use, age or gender.

Conclusion

Some patients with narcolepsy have deficient hypocretin neurotransmission. Since other studies have documented hypocretin receptor and peptide gene alterations producing narcoleptic like conditions in animal models, hypocretin deficiency can be seen as also contributing to the development of narcolepsy in humans.

☆ Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficfiency in human narcolepsy. Lancet 2000;355:1096–1100.

PII: S1389-9457(00)00016-2

Comment

This is a straightforward study with a very clear and critical result. The results are consistent with the prior extensive work in animal models. There can be little doubt that hypocretin deficiency relates to human narcolepsy. It is noted that the diffuse projections of the hypocretin system include substantial projections to monoaminergic cell groups and may serve to decrease monoaminergic tone, thereby producing the symptoms of narcolepsy.

While hypocretin appears to be central to human narcolepsy it seems unlikely that this results from a highly penetrant hypocretin mutation since, unlike the canine model, narcolepsy is rarely familial. Thus the authors speculate that the hypocretin cells are either destroyed or made non-functional by some HLA-associated autoimmune-mediated process. The argument supporting an elemental role of hypocretin deficiency in the pathophysiology of narcolepsy is complicated by the two patients who did not exhibit low hypocretin levels. As the authors suggest there may be other conditions which deactivate the hypocretin system such as receptor/effector mediated deficiency. Disturbances in hypocretin-2 and other proteins that may contribute to this pathway may also be involved. It is certainly not unusual to discover multiple pathways producing the same neurological deficit leading to the clinical disorder.

Hypocretin deficiency clearly seems to contribute to narcolepsy. It now remains to discover whether or not activating the hypocretin system can be done and can provide a new approach to treatment for narcolepsy.