

SHORT REPORT

Hypocretin (orexin) deficiency in narcolepsy and primary hypersomnia

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The discovery that hypocretins are involved in narcolepsy, a disorder associated with excessive daytime sleepiness, cataplexy, and unusually rapid transitions to rapid eye movement sleep, opens a new field of investigation in the area of disorders of sleep and activation. Hypocretin-1 (hcrt-1) and hypocretin-2 (hcrt-2) (also called orexin-A and orexin-B) are newly discovered neuropeptides processed from a common precursor. Hypocretin containing cells are located exclusively in the lateral hypothalamus, with widespread projections within the central nervous system. The role of the hypocretin system in other disorders causing excessive daytime sleepiness is more uncertain. This study reports the findings of a prospective study measuring cerebrospinal fluid concentrations of hypocretin-1 and hypocretin-2 in HLA DQB1*0602 positive narcolepsy with cataplexy, monosymptomatic narcolepsy, and primary hypersomnia. The results confirmed the previous observations, that hcrt-1 is deficient in narcolepsy and for the first time report very low levels of hcrt-1 in primary hypersomnia. It is also reported for the first time that there is a generalised defect in hcrt-2 transmission in all three of these clinical entities compared with controls.

The hypocretins (orexins) are recently described hypothalamic neuropeptides thought to play a significant part in the regulation of sleep and arousal states. Their discovery was reported by two groups, independently, and using different techniques.^{1–3} The terms, orexin and hypocretin used by the two groups are synonymous and for the purposes of this article we will use the term hypocretin (Hcrt). The finding that cerebrospinal fluid (CSF) concentrations of hcrt-1 were abnormal in patients with narcolepsy has stimulated research on the potential role of these peptides in disorders of sleep and activation.⁴

Narcolepsy is a sleep disorder with a prevalence of 1 in 2000 adults, it usually appears between the ages of 15 and 30 years and shows a mixture of four characteristic symptoms: (1) excessive daytime sleepiness (EDS), with irresistible sleep attacks during the day; (2) cataplexy (brief episodes of muscle weakness or paralysis precipitated by strong emotion, such as laughter or surprise); (3) sleep paralysis, the persistence of REM atonia in wakefulness; (4) hypnagogic hallucinations or dream-like images, which characteristically occur at sleep onset. EDS is a prerequisite for the diagnosis and the presence of cataplexy secures the clinical diagnosis. Cataplexy usually develops within two years of the onset of EDS but may take up to two decades to manifest.⁵

HLA typing reveals the DQB1* 0602 subtype in 90% of people with narcolepsy compared with 12%–38% of controls, but the possession of this allele is neither necessary nor sufficient for the disorder.^{5,6} Overnight polysomnography helps to rule out other causes of excessive sleep disorder, such as

obstructive sleep apnoea. The multiple sleep latency test (MSLT) generally shows reduced mean sleep latency and the occurrence of episodes of sleep onset rapid eye movement within 15 minutes of sleep onset.

The presence of the symptoms of narcolepsy in the absence of cataplexy is referred to as monosymptomatic narcolepsy (MN) (narcolepsy without cataplexy). It is thought that up to 60% of patients with MN progress to narcolepsy-cataplexy (NC).⁶

It has been suggested that disruption of hypocretin neurotransmission causes human narcolepsy and that CSF hcrt-1 measures could be used as a diagnostic tool for narcolepsy.⁷ The initial report, and subsequent replication study, found most HLA positive patients with NC had undetectable concentrations of CSF hcrt-1.^{4,5,7,8}

Primary hypersomnia (PH, also known as idiopathic hypersomnia) is characterised by EDS, but without cataplexy or nocturnal sleep disruption. It usually starts in adolescence and is of unknown aetiology. Patients with this disorder report increased total sleep times. No amount of sleep improves the EDS and naps are frequently unrefreshing (unlike narcolepsy where naps are reported to be refreshing). Polysomnography usually reveals a shortened sleep latency, increased total sleep time, and, reduced sleep latency on the multiple sleep latency test.⁹ There is an absence of sleep onset REM periods. Much less is known about the potential role of hypocretin and its neurotransmission in PH.⁹

To date, there have been no published reports on CSF hcrt-2 concentrations in humans.

This study was undertaken firstly to measure CSF hcrt-1 in a sample of patients with NC in our population and to confirm that abnormal hypocretin neurotransmission is a characteristic feature of NC. Secondly, to measure CSF hcrt-1 concentrations, in MN and PH, and, thirdly, to evaluate the possible role of hcrt-2 in these disorders of sleep and activation.

METHODS

Volunteers for the study were recruited from the outpatient clinic list of the Sleep Disorders Centre at St Thomas's Hospital, London. All subjects gave informed consent for the study, which had been approved by our local ethics committee.

Patient assessments included the following: Epworth Sleepiness Score (ESS); clinical evaluation by a senior sleep physician (AJW) and HLA typing; conventional nocturnal polysomnography; MSLT.

Diagnostic criteria

NC was diagnosed by the presence of EDS >6 months, an ESS >10, and the presence of cataplexy. MN was diagnosed using

Abbreviations: Hcrt, hypocretin; EDS, excessive daytime sleep; NC, narcolepsy-cataplexy; CSF, cerebrospinal fluid; MN, monosymptomatic narcolepsy; PH, primary hypersomnia; MSLT, multiple sleep latency test

Table 1 CSF hypocretin concentrations in narcolepsy and primary hypersomnia

Diagnosis	Sex	Age	Years since onset	HCRT-1 (pg/ml)	HCRT-2 (pg/ml)	HLA DQB1*0602
NC	F	23	5	ND	3.27	+
	F	54	21	ND	2.94	+
	F	33	7	ND	2.97	+
	F	33	6	ND	3.34	+
	F	26	10	ND	7.01	+
	F	55	25	ND	5.01	+
	F	27	16	ND	9.69	+
	F	65	30	ND	5.01	+
	F	22	8	ND	3.34	+
	F	68	32	ND	2.51	+
	F	19	5	ND	4.34	+
	F	29	20	ND	3.67	+
	M	25	2	ND	3.34	+
	M	50	12	ND	4.01	+
MN	F	56	22	50.10	5.68	+
	F	57	42	43.42	0	+
	F	35	16	46.76	3.14	+
	M	39	6	50.10	2.64	-
IH	F	55	26	86.84	9.35	-
	F	40	12	73.48	11.36	-
	M	55	7	53.44	3.01	-
	M	44	27	73.48	6.68	-
	M	29	9	63.46	4.68	-
	M	32	13	56.78	7.35	+
Controls	M=5, F=19	36 (6)*	NA	210 (46)*	9.4 (7.9)*	NA

ND, not detectable. * mean (SD).

the following criteria: EDS >6 months; ESS >10; no cataplexy; sleep latency <10 minutes; MSLT with >1 sleep onset REMs; no other evident cause(s) of EDS and Apnea-Hypopnea Index (AHI) <10; no improvement in EDS after sleep extension. PH was diagnosed in patients who fulfilled the criteria for MN but who had no sleep onset REMs.

CSF samples were collected between 10 am and 11.30 am, immediately frozen, coded, and transported to the laboratory. Radioimmunoassay kits (Phoenix Pharmaceuticals, Mountain View, CA) were used to measure hcrt-1 and hcrt-2 concentrations as previously reported.⁴

Statistical analysis

In addition to a standard descriptive statistics, we used two way analysis of variance and paired *t* test to examine data relations.

RESULTS

Control group

CSF samples were obtained from stocked samples previously taken for research purposes. The control group of 24 was subdivided as follows: 19 women, five men; median age 36.4 years, range 21.2–47.3. Thirteen of the 24 control CSF samples were drawn from epidural taps of women in labour. The remaining 11 were obtained from patients presenting with neurological symptoms without any organic basis (conversion disorders). In keeping with previously reported data in control groups, hcrt-1 was detectable in all the control samples with a mean (SD) of 210 (32) pg/ml.^{5–9,12} Hcrt-2 was detectable in all the CSF samples of the control group (mean (SD) of 9.44 (7.85) pg/ml; range: 2–43 pg/ml).

Study group

The study group comprised 24 patients (17 women, seven men (M), median age 36.5 years, range 19.1–67.5). NC was diagnosed in 14 patients (12 women, two men), MN was diagnosed in four patients (three women, one man), and in six patients (two women, four men) a diagnosis of PH was made.

Narcolepsy-cataplexy

Sleep study assessments in this group revealed ESS results broadly in keeping with that expected with a mean score of 19.6. MSLT analysis (n=13, one patient was unable to complete a sleep study) revealed a mean sleep latency of 3.9 minutes. All the patients with NC were HLA DQB1*0602 positive. The group's mean body mass index (BMI) was 31.1 (6.2) kg/m², similar to previous published findings.⁸ CSF hcrt-1 was below the detection limit (40 pg/ml) in all the patients with NC and the mean CSF hcrt-2 concentration was 4.32 (1.93) pg/ml.

Monosymptomatic narcolepsy

This group scored a mean of 18 on the ESS with the MSLT analysis revealing a mean sleep latency of 5.4 minutes. Three of four patients were HLA DQB1*0602 positive. The mean BMI was 25.6 (5.24) kg/m². Very low values of CSF hcrt-1 were found in patients with MN (n=4; mean=48 (3pg/ml)) and CSF hcrt-2 concentrations were mean 2.86 pg/ml (2.33) pg/ml. Hcrt-2 was completely undetectable in a single patient with MN who was indistinguishable from the others on clinical and NPSG criteria.

Primary hypersomnia

Patients in this group had a mean ESS score of 18 and a mean sleep latency of 5.7 minutes. A single patient with PH was also HLA DQB1*0602 positive. The mean BMI was 22.7 (1.2) kg/m². The mean CSF hcrt-1 was 67.9 (12.4) pg/ml whereas the mean CSF hcrt-2 concentration was 7.1 (3) pg/ml.

Analysis for the entire sample revealed a mean sleep latency (n=23) of 4.6 minutes. BMI measures showed a mean (SD) of 28.1 (6.3) kg/m². There was no demonstrable correlation between CSF hcrt-1 concentrations and ESS or sleep latency in the group as a whole and in each subgroup. The mean CSF hcrt-2 was 4.8 (2.6) pg/ml and a range of 0–11 pg/ml.

Statistical analysis using two way analysis of variance and paired *t* test for means reveals that the differences observed in CSF hcrt-2 concentrations between the control and study

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The British Neuropsychiatry Association 2003 Annual Meeting

The British Neuropsychiatry Association 2003 Annual Meeting will be held at the Institute of Child Health, central London on 13–14 February 2003. The meeting will cover the topics: "Recovering from head injury", "Medico-legal aspects of neuropsychiatry", and "The neuropsychiatry of love (A feast for Valentine's Day)". The meeting includes keynote addresses from prominent international and UK speakers, along with a session for members' contributions.

Additionally, on 12 February 2003, BNPA are holding a conference sponsored by the Institute of Social Psychiatry on "Stepping out after brain injury"; this will be linked to the BNPA conference session on "Recovering from head injury".

For further information please contact: Gwen Cutmore, BNPA Conference Secretary, Landbreach Boatyard, Chelmer Terrace, Maldon, Essex CM9 5HT (tel/fax: +44 (0)1621 843 334; email: gwen.cutmore@lineone.net; website: www.bnpa.fsnet.co.uk).

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