Sleep—wake stability in narcolepsy patients with normal, low and unmeasurable hypocretin levels

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Objective: To compare diurnal and nocturnal electrophysiological data from narcolepsy patients with undetectable (<20 pg/mL), low (20–110 pg/mL) and normal (>110 pg/mL) cerebrospinal fluid (CSF) hypocretin-1 levels.

Patients/Methods: A total of 109 narcolepsy patients and 37 controls were studied; all had available CSF hypocretin-1 measurements. The sleep laboratory studies were conducted between 2008 and 2014. The study retrospectively examined measurements of sleep stage transitions in diurnal and nocturnal continuous polysomnography. The percentage distribution of time awake and rapid eye movement (REM) sleep, and the occurrence of sleep onset REM (SOREM) in the nocturnal polysomnography were also measured.

Results: Participants with undetectable hypocretin-1 levels had significantly higher frequencies of transitions than controls and those with normal hypocretin-1 levels. Participants with low hypocretin-1 levels showed more transitions than controls and, in some cases, also more than those with normal hypocretin-1. Participants with normal hypocretin-1 failed to show any significant difference from the controls, except in the overall diurnal transitions.

Conclusion: Undetectable hypocretin-1 levels in particular, but also low hypocretin-1 levels, were associated with a less stable phenotype featuring more sleep state transitions and SOREM episodes. In addition, there was a distinction between nocturnal and diurnal REM sleep in hypocretin-deficient participants, expressed as increased diurnal REM sleep, which was not reflected in nocturnal sleep.

Statement of significance

During clinical evaluation of narcolepsy, electrophysiological data are obtained from polysomnography (PSG) and the Multiple Sleep Latency Test (MSLT). Only a small amount of this information is used. The present study showed that sleep—wake instability can be quantified from PSG data, and that lower hypocretin levels in cerebrospinal fluid are associated with greater instability. This provides a possible objective measurement of disease severity. The study showed that hypocretin-deficient patients have especially pronounced instability of wakefulness and sleep during the day. In addition, these patients have increased diurnal REM sleep, but no increase in nocturnal REM sleep, indicating the presence of a general diurnal REM sleep pressure that individuals with normal hypocretin levels do not experience.

1. Introduction

Narcolepsy is a chronic neurological sleep disorder, with a prevalence of one per 2000–5000 individuals, that typically debuts in childhood and adolescence [1–3]. The disease causes multiple morbidities, as well as having social and economic consequences [4]. The recent classification of sleep disorders [5] divides narcolepsy into two subgroups: Type I (NT1) and Type II (NT2). Type I is
defined by excessive daytime sleepiness (EDS) of >3 months combined with either hypocretin-1 (hcrt-1) levels ≤110 pg/mL or the presence of cataplexy combined with a pathological Multiple Sleep Latency Test (MSLT) result (mean sleep latency <8 min and ≥2 sleep onset rapid eye movement (SOREM) episodes). Type II (NT2) is defined by EDS of >3 months duration, a pathological MSLT result and the absence of other more likely explanations for the symptoms. The finding of a low level of hcrt-1 due to selective destruction of hypocretinergic neurons in the lateral hypothalamus [6] is essential for understanding the pathophysiology of NT1, whereas knowledge of the pathophysiology of narcolepsy with normal hcrt-1 levels (NT2) is limited [7,8].

Sleep–wake regulation consists of sleep-promoting and wake-promoting pathways. The wake-promoting pathways (the ascending arousal system) include the thalamus and provide direct involvement of the hypothalamus, basal forebrain and cerebral cortex. The main sleep-promoting pathways arise from the hypothalamus and inhibit the components of the ascending arousal system. Furthermore, the ascending arousal system is capable of mutually inhibiting the sleep–promoting pathways. Rapid eye movement (REM) sleep is regulated by two mutually inhibitory groups of neurons in the upper pons: the REM-on and REM-off neurons [8,9]. Hypocretinergic neurons play an important role in stabilising these two systems and thereby wakefulness and sleep. In addition, hcrt-1 appears to stabilise the different sleep states, ensuring a continuous regular sleep pattern, and is involved in motor control [11,12]. As expected, hcrt-1 deficiency is therefore followed by numerous problems such as: instability of sleep and wakefulness, resulting in sudden sleep episodes from wakefulness; instability of REM-sleep, resulting in SOREM, increased sleep transitions, sudden loss of motor tonus (cataplexy), and nocturnal REM sleep without atonia [13].

Previous studies have demonstrated increased nocturnal sleep instability in NT1 patients [11,14,15]. One study included diurnal sleep, counting nap frequency, SOREMPs, total sleep time, and time in each sleep state [14]. Another study compared patients with different degrees of hcrt-1 deficiency using data from nocturnal actigraphy [15]. However, neither the diurnal sleep transitions, nor the influence of the degree of hcrt-1 deficiency on polysomnographic data have ever been properly evaluated. The present study aimed to describe the critical role of hcrt-1 in regulating wakefulness and sleep during spontaneous diurnal and nocturnal sleep. It also investigated whether different levels of hcrt-1 deficiency are of importance to the clinical phenotype.

2. Methods

2.1. Participants

Patients were retrospectively included following an evaluation of all patients who had undergone a lumbar puncture at the Danish Center of Sleep Medicine (DCSM) between 2008 and 2014 (and a single patient who received one in 2007), giving a total sample of 543. A further inclusion criterion required the diagnosis of type I or II narcolepsy, as determined by the International Classification of Sleep Disorders, third edition (ICSD-III) [5] criteria for narcolepsy, which yielded a final sample of 109 participants.

Participants were divided into three subgroups depending on their hcrt-1 levels: hcrt-1 levels <20 pg/mL, referred to as undetectable hcrt-1 (NT1a); hcrt-1 levels between 20 and 110 pg/mL, referred to as low hcrt-1 (NT1b); and hcrt-1 levels >110, referred to as normal hcrt-1 (NT2). The cut-off of 20 pg/mL was chosen, as this is the lowest level that the present laboratory can detect.

Cataplexy was present in: 33 out of 35 NT1a participants, 28 out of 32 NT1b participants, and four out of 42 NT2 participants (three of these had hcrt-1 levels between 110 and 200 pg/mL). HLA measurements were unavailable.

Ninety-two participants had no additional neurological or psychiatric disorders. The other 17 had the following comorbidities: two had previously suffered a stroke, two were diagnosed schizophrinic, one had Asperger’s disease, one had dystrophia myotonica type I, one had Parkinson’s disease, one had juvenile myoclonic epilepsy, one had EMG-confirmed sensory polyneuropathies, six were receiving treatment for depression, and two were being treated for anxiety. Twenty-one of the 109 participants had sleep apnoea (14 mild, two moderate, five severe), 11 of which had undetectable hcrt-1 levels (six mild, one moderate, four severe), five had low hcrt-1 levels (three mild, one moderate, one severe) and five had normal hcrt-1 levels (all mild).

All participants were requested to discontinue use of antidepressants and central nervous system stimulants 4–14 days before polysomnography (PSG). They were also advised to adopt a stable sleep schedule seven days before the PSG.

The control group consisted of 37 individuals with subjective complaints of sleepiness, but without any sleep disorders, as evaluated by an MSLT, PSG, lumbar puncture and a diagnostic interview with a physician. The demographic data of the participants are summarized in Table 1.

2.2. Data

The CSF-hcrt-1 level was measured in all participants according to the protocol described by Knudsen et al. [16]. A total of 110 of the PSGs were performed in accordance with the American Academy of Sleep Medicine (AASM), and 36 in accordance with the method of Rechtschaffen and Kales (R&K), both using the Nicolet™ (Nervus) PSG/EEG (Natus – Nicolet brand products, Middleton, WI, USA). Polysomnography data were available for all 146 cases. The PSG recordings were continuous throughout the day and night, and participants were only disconnected when visiting the bathroom. The starting time of the recordings differed, but they were all terminated at 07:00 the next morning, and the average length of the recordings was 1087.3 min. All records were divided into diurnal and nocturnal periods, indicated by the time the participants turned out the lights, which was between 21.30 and 23:00.

For further evaluation of the sleep state transitions, data were extracted and all transitions between the 30-s epochs in the hypnogram were counted. This produced a 3 × 3 transition matrix, as shown in Table 2. The states were defined as wake, REM sleep and non-REM (NREM) sleep, and a transition was thus defined as the shift from one 30-s epoch to the next one. Due to the differences in the total recording time of the PSGs, the frequencies of the transitions were measured as transitions per hour. The transitions included were: total transitions from one of the three states to another type of state, between wake and sleep, from wake to REM sleep, between NREM sleep and REM sleep, and from REM sleep to REM sleep. The percentage distribution of wake and REM sleep, and

<table>
<thead>
<tr>
<th>Table 1 Demographic data of participants.</th>
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<tr>
<td>hcart-1 &lt;20 (undetectable)</td>
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<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Male/female</td>
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<tr>
<td>Age (years)*</td>
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<td>BMI (kg/m²)</td>
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Age and BMI are given as the mean ± standard deviation. BMI, body mass index; hcart-1, hypocretin-1.

* Age at the time of the polysomnographic recording hcart-1 is measured in pg/mL.
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