Narcolepsy beyond sleepiness : endocrine, metabolic and other aspects

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General introduction and aim of the thesis

Based on 'Clinical and pathophysiological aspects of narcolepsy'.
International Journal of Sleep and Wakefulness 2007; 1(2):55-65.

INTRODUCTION

Narcolepsy with cataplexy is a chronic sleep disorder caused by hypocretin deficiency, that affects approximately 25–50 per 100,000 people.[1] The first symptoms usually appear from childhood to midlife with a large peak around 15 years of age and a smaller one around 36.[2] It has a profound effect on the quality of life[3] that might exceed the burden of other serious chronic diseases like epilepsy.[4] Narcolepsy is associated with reduced vigilance,[5] severe fatigue,[6] anxiety and mood disorders[7] and a higher rate of car accidents.[8-10] In addition the unemployment rate among patients is higher than in controls.[11]

SIGNS AND SYMPTOMS OF NARCOLEPSY

Excessive daytime sleepiness

The excessive daytime sleepiness (EDS) may come in various forms, with a continuous feeling of sleepiness at one end of the spectrum, and sudden involuntary and irresistible "sleep attacks" at the other. Narcolepsy patients often experience a combination of these. Daytime sleep episodes are brief, often < 20 min, and are typically reported to be refreshing. Although sleep episodes may occur several times a day, the total amount of sleep is not or only slightly increased over a 24-h period due to nocturnal sleep fragmentation.[12]

Nocturnal sleep disturbances

Fragmented nocturnal sleep is a major and common problem in narcolepsy. While patients fall asleep very quickly numerous awakenings may follow. These awakenings are usually short but can sometimes last for hours, forcing patients to get out of bed. Importantly, fragmented night-time sleep is not the cause of EDS; while improving nocturnal sleep may sometimes alleviate daytime sleepiness, EDS will never disappear.[13]

Cataplexy

The most specific symptom of narcolepsy is cataplexy, derived from the Greek word καταπλησσω meaning "to strike down". Cataplexy is defined as a sudden bilateral loss of muscle tone with preserved consciousness, usually triggered by emotions. The combination of cataplexy and EDS is pathognomonic for narcolepsy. Cataplexy can be triggered by a

diversity of emotions. The most often reported triggers are laughter, hearing a joke, or feeling excited. Although most cataplectic attacks do have a trigger, 40% of the patients have experienced attacks without an identified trigger. Most cataplectic attacks are partial, resulting for example in sagging of the jaw with blurred speech or buckling of the knees. Partial attacks may evolve into a complete loss of skeletal muscle tone leading to a fall but, because of its gradual onset, patients can usually support themselves preventing injury.[14]

Hypnagogic hallucinations

Hypnagogic hallucinations are vivid dreamlike experiences that occur upon falling asleep. The auditory, visual, or tactile sensations are usually felt to be real, and are often bizarre and frightening. The perception of intruders, with people or animals standing over or lying under the bed is a common reported phenomenon.[15]

Sleep paralysis

Sleep paralysis is the inability to move at sleep onset or, more commonly, when awakening.[16] While the patient is awake, it is impossible for them to move their arms or legs or sometimes even open their eyes, and it can be extremely distressing, especially when occurring for the first time. It often occurs in combination with hypnagogic hallucinations. About half of the patients experience sleep paralysis. This phenomenon is much less common where it only affects 5% of the population.[17]

ADDITIONAL SIGNS AND SYMPTOMS OF NARCOLEPSY

In addition of the above mentioned symptoms, there are various other features, frequently seen in narcolepsy patients. A few of them, most relevant for this thesis will be discussed.

Obesity

It has long been known that the majority of the narcolepsy patients tend to be overweight. This was usually attributed to inactivity due to EDS and received little attention. However, more recent epidemiological studies have clearly shown that overweight is a major symptom of narcolepsy.[18-20] Obesity (body mass index [BMI] ≥ 30 kg/m^2) occurs more than twice as often in patients with narcolepsy as among the general population. The cause of weight gain

in narcolepsy is unknown. Some patients complain about a tendency to binge eat, especially during waking periods at night. However, in a study using cross-checked dietary histories, it was shown that over a period of 24 h individuals with narcolepsy tended to consume fewer calories than controls, particularly carbohydrates.[21;22] Patients with idiopathic hypersomnia have been shown to have a lower BMI than narcoleptics, indicating that inactivity due to EDS is not likely to account for the obesity.[18] It seems possible that mechanisms such as a lowered metabolic rate underlie the increase in body weight seen in subjects with narcolepsy.

Temperature differences

Narcolepsy patients have an altered thermoregulatory profile with warmer hands and feet and lower proximal skin temperature than controls, a state in which sleep propensity is high.[23] Temperature manipulation studies offsetting these temperature changes show improvement in narcolepsy symptoms.[24;25]

Memory complaints

Many narcolepsy patients have memory complaints. Interestingly, when formally tested, they do not always show objective memory deficits.[26;27] The reason for this is unclear; patients may, for example, be more vigilant in a testing situation than in everyday life.

Delusional confusion of dreaming and reality

Narcolepsy patients may report difficulty distinguishing between dreams and reality. However, although frequently heard in the consulting room, it is rarely mentioned in the literature. So far just a few case reports have described more severe examples of memory source confusion in patients suffering from narcolepsy, in which false accusations of sexual assault occurred when patients mistook a dreamed assault for the memory of an actual event.[28;29]

Endocrine alterations

The most prominent hormonal disturbances in human narcolepsy were found in leptin, and the somatotropic axis. Serum concentrations of the adipocyte-derived hormone leptin were found to be significantly lower, and the daily fluctuations in leptin levels were absent in narcolepsy.[30;31] However, others found normal leptin levels in a single sample study in a

larger group of narcolepsy patients.[32;33] For the somatotropic axis, the circadian secretion of GH appears to be altered, so that a relatively large fraction of total production occurs during daytime in narcoleptics.[34] In addition, 24-h thyrotropin (TSH) levels were reduced in narcolepsy patients. In contrast, thyroxin (T4) and triiodothyronin (T3) were normal, so the clinical relevance of these findings remains to be elucidated.[35] A blunted total and basal adrenocorticotropic hormone (ACTH) production was found in narcolepsy patients whereas the pulsatile secretion was normal[35] which seemed to indicate that hypocretins are involved in the basal but not pulsatile secretion of ACTH. The circadian rhythm of cortisol and ACTH was normal, showing that the circadian timekeeper is intact in narcolepsy. Finally, a role for hypocretin-1 in luteinizing hormone (LH) release was observed in rats.[36] Accordingly, a decreased 24-h mean LH concentration and pulsatile secretion was found in human hypocretin deficiency.[37] A high prevalence of precocious puberty is found in children with narcolepsy.[38]

Diabetes

In the sixties and eighties some reports have been published on a higher incidence of insulin resistance and type II diabetes mellitus (T2DM) in narcolepsy.[39-41] Another study confirmed a higher risk of metabolic syndrome independent of BMI by comparing narcolepsy patients to idiopathic hypersomnia patients.[22] However, in a recent study where a large group of patients were compared to healthy matched controls, no differences in insulin resistance were found by calculating pro-insulin to insulin ratio and using homeostatic model assessment method (HOMA).[42] Unfortunately in the last study, patients were medicated. This might have influenced the results. Anticataplectic drugs e.g. imipramine may produce a significant increase of fasting blood glucose levels.[43]

PATHOPHYSIOLOGY OF NARCOLEPSY

Hypocretin deficiency

The finding that hypocretin (orexin) knockout mice had symptoms of narcolepsy[44] and the nearly simultaneous report that genetically narcoleptic canine narcolepsy was caused by a mutation in the Hypocretin-2 receptor[45] led to the hypothesis that human narcolepsy might be due to a malfunction of the hypocretin system. This hypothesis was supported by the finding of greatly reduced levels of hypocretin in the cerebrospinal fluid of human narcoleptics.[46]

Two simultaneously published papers from different laboratories then reported a loss of hypocretin cells in brains of human narcolepsy patients.[47;48] Peyron et al. also reported a single case of early onset narcolepsy associated with by a hypocretin mutation. Thannickal et al. reported elevated levels of gliosis in the hypothalamic region where hypocretin cells had been lost, consistent with the autoimmune hypothesis.[48;49] Further work showed that the number of hypothalamic neurons containing dynorphin and Narp, both substances known to be localized to hypocretin cells, were reduced by 90% in narcoleptics with cataplexy.[50;51] This finding suggests that hypocretin cells are lost, rather than simply being unable to produce hypocretin.

Autoimmune hypothesis

Several lines of evidence point to an autoimmune origin for most cases of human narcolepsy. Honda discovered that nearly all Japanese narcoleptics had an HLA type (DR2, in the then standard terminology), whereas only 20–30% of the non-narcoleptic population had this haplotype.[52] Since the HLA molecules function to present antigen to the immune system, this finding suggested that the immune system was involved in the genesis of narcolepsy. A narcolepsy linkage to HLA-DQA1*01:02 and -DQB1*06:02 was demonstrated.[53] An association was demonstrated between narcolepsy and polymorphisms in the T-cell receptor alpha locus in a genome-wide association study.[54] Further evidence for the autoimmune hypothesis includes the initially disputed report that streptococcal antibodies were often elevated in narcoleptics,[55;56] with Montplaisir et al.'s initial observations recently replicated.[57] An anecdotal report of rapid onset of narcolepsy with cataplexy after an anaphylactic reaction to an insect bite[58] further supports this hypothesis. Additionally, the discovery of circulating TRIB2-specific antibodies reactive to hypocretin neurons in individuals with narcolepsy,[59-61] strongly suggest an autoimmune nature. Although this is a major breakthrough in narcolepsy research, the role of TRIB2 antibodies remains unclear and there is no direct proof that these antibodies actually damage hypocretin neurons.[62] Recent reports of an association of narcolepsy onset with immunization for the H1N1 flu[63] or H1N1 flu infection[64] supports the autoimmune hypothesis as well, although some of this evidence is disputed.[65] The latest paper demonstrates CD 4 T cell involvement and seemed to get closer to prove the autoimmune hypothesis.[66] Unfortunately the paper got retracted because the results could not get replicated. Although there are very strong indications for an autoimmune cause of narcolepsy, the exact mechanism of disease onset remains to be elucidated.

TREATMENT OF NARCOLEPSY

Every narcolepsy patient should be advised to live a regular life, trying to have similar bedtimes every day. Scheduled naps can alleviate sleepiness for a while, and may be advised.[67] Likewise, a short nap before demanding activities may be helpful. However, in the majority of patients, pharmacological treatment is necessary.[15;68] In practice, it is recommended to start treating the most disabling symptom first, and to tailor drug schedules and dosages individually. Combination therapy is often necessary.[68] It must be emphasized that drug therapy is purely symptomatic. While cataplectic attacks can often be completely abolished, EDS will never completely disappear. Drugs to treat narcolepsy are usually divided into two groups; stimulant drugs to treat EDS and anti-cataplectic drugs that also tackle dream related symptoms.

Stimulants

Examples of wake promoting agents are amphetamines, and amphetamine like drugs e.g. methylphenidate. The mode of action of these drugs is complex, but the central mechanism entails the enhancement of the release of catecholamines (dopamine and noradrenaline) as well as uptake inhibition.[69;70] A frequently prescribed non-amphetamine like substance is modafinil. Its mode of action is still a matter of debate. Several studies indicate that modafinil, like other stimulants, inhibits the reuptake of dopamine (DA) via the DA transporter (DAT).[71] However in vitro studies show that modafinil binds to the DAT with lower affinity than methylphenidate and other psychostimulants drugs.[71] Recent research identified several non-dopaminergic effects of modafinil, such as the increase of electrical neuronal coupling, or the enhancement of histamine and orexin neurotransmission that might be of primary importance to explain its efficacy as a wake-promoting and cognitive-enhancing medication.[71]

Anticataplectic drugs

In general, the amelioration of cataplexy is associated with a reduction of hypnagogic hallucinations and sleep paralysis. Tricyclic antidepressants are among the most effective agents, often in even very low doses.[68] Those most commonly used include imipramine, and clomipramine. In contrast to the tricyclics, SSRIs usually require a relatively high-dose, which can sometimes negate their more favorable side-effect profile. Venlafaxine, a noradrenalin/serotonin reuptake inhibitor, might have some beneficial effect on cataplexy too, although

publications on its efficacy are scarce. Acute withdrawal from antidepressants may severely aggravate cataplexy, sometimes leading to a status cataplecticus (sequential cataplexy attacks that may last for hours or even longer).

Sodium oxybate

A more recently approved compound to treat narcolepsy is sodium oxybate (SXB,γ-hydroxybutyrate; GHB). SXB is a hypnotic and is taken twice a night (at bedtime, and a second dose 3–4 hours later). Interestingly, despite the short half-life of the drug and its nighttime administration, the effects on daytime cataplexy are already obvious when using low dosages (3–6 gr/night).[72] Additional studies show that the use of higher doses of SXB (up to 9 gr/night) has additional positive effects on the excessive daytime sleepiness, and the quality of nocturnal sleep.[73] Moreover SXB may reduce weight, a side effect that could be beneficial to an overweight patient.[74] GHB occurs naturally in the brain, but its mechanism of action in narcolepsy is not precisely known. In healthy subjects, it was shown that administration of SXB has a slow wave sleep (SWS) promoting effects associated with an increase in GH secretion.[75] Its effects are thought to be mediated through γ-aminobutyric acid B receptor (GABAB) and has an impact on dopamine and serotonin release.[76;77] The existence of a specific GHB receptor is still under debate.

AIM OF THE THESIS

The first part of the thesis consists of a number of endocrine studies in hypocretin deficient male narcolepsy with cataplexy patients. Hypocretins are, besides their crucial function in the regulation of the sleep-wake cycle, involved in food intake, glucose sensing and homeostasis, and in virtually all endocrine axes.[78] Accordingly metabolic and hormonal disturbances are increasingly recognized as important features of narcolepsy.[22;30;35;37;38] Therefore, it may be very important to find treatment options that also deal with these aspects. SXB may very well be a suitable candidate, as the drug activates dopaminergic circuits in the brain where diminished dopamine (D2) receptor mediated signal transduction appears to induce insulin resistance, the metabolic syndrome and diabetes mellitus type 2.[79] If SXB is indeed able to reduce insulin resistance, it may also have an important impact on metabolic disturbances in obese patients without narcolepsy. In addition, more and more evidence suggests that GHRH, the hypothalamic hormone controlling the release of GH, simultaneously promotes the occurrence of non-REM sleep as well as GH release.[80] On the basis of these

data, it has been hypothesized that SXB may act by stimulating the GHRH secretion in the central nervous system and thereby promoting SWS and the release of GH.[75] When administered during nocturnal sleep in narcoleptics, it may again confine GHRH secretion to the night and decrease possible sleep inducing effects of GHRH as a consequence of daytime release.

Part I Endocrine studies in narcolepsy

The objective is to investigate whether the secretion of Prolactin (PRL) (chapter 2), Growth Hormone (GH) (chapter 3), Leptin and Ghrelin (chapter 4), and Melatonin (chapter 5) is altered in narcolepsy patients compared with individually matched healthy controls. In addition, the effect of short term administration of SXB on the aforementioned substances is described.

Earlier reports on PRL secretion in narcolepsy patients have been inconclusive, showing either increased, decreased or normal levels.[81-83] Discrepancies seemed to be due to methodological issues. The major physiological regulator of PRL release is dopamine.[84] Alterations in the dopaminergic system in the post-mortem brains of narcoleptics have been described making changes in PRL release in narcolepsy conceivable.[85] Although the exact mode of action is still unclear, SXB acts on gamma-aminobutyric acid type B (GABAB) and has an impact on dopamine and serotonin release.[77] Therefore, SXB treatment may be expected to alter PRL secretion. We hypothesised that changes in hypothalamic hypocretin signaling in narcoleptic patients may give rise to altered PRL secretion. In addition, we aimed to determine the effect of SXB administration on PRL secretion and sleep, both in a healthy and in a hypocretin-deficient state.

In healthy subjects, there is a clear association between GH secretion and SWS. This is especially clear in young males, in which the majority of 24-h GH is secreted during the first period of SWS at night.[75] It has been shown previously that GH secretion was less strictly confined to the night in narcolepsy patients.[34] As the relation between SWS and GH secretion was preserved, it was suggested that a shift of SWS episodes to the day was paralleled by a daytime shift of GH secretion. In contrast to other hypnotics, SXB is one of the few compounds that increases rather than decreases SWS. This led to the hypothesis that it may also act as a GH secretagogue. Indeed, it has been shown that single-dose SXB administration leads to an increase in GH secretion in healthy young men, paralleled by an increase in SWS.[75] Here we explore whether SXB administration leads to an increase in nocturnal GH secretion in both patients and controls, paralleled by an increase in SWS.

Leptin and ghrelin are both strong regulators of energy homeostasis, and their relationship with hypocretin has been shown to be of importance. Receptors for leptin are found on hypocretin cells,[86] and leptin can directly inhibit the expression of isolated hypocretin neurons.[87] Indirectly, leptin can affect the activity of hypocretin cells via energy-regulating neurons in the arcuate nucleus of the hypothalamus.[88] Ghrelin is an important endogenous regulator of energy balance and it excites hypocretin neurons. An interaction between these two systems has been shown to be involved in ingestive behavior.[87] Its expression is complex[89] and influenced by sympathetic nervous system activity.[90] Across the wake period, plasma concentrations wax and wane episodically, providing an appetite-stimulating signal to the brain.[91] Hypocretin neurons directly sense ghrelin and leptin but it is unknown if these connections are uni-or-bidirectional.[92] Therefore a study of hypocretin deficient narcolepsy patients provides a unique opportunity to explore the nature of these relationships. In addition we hypothesized that SXB administration would alter total ghrelin levels, which might be involved in its GH-promoting effects.

Melatonin is a modulator of sleep and high levels induce sleepiness.[93] Animal models indicate that the hypocretinergic innervation of the pineal gland could be important for the regulation of diurnal melatonin synthesis and secretion.[94] It is therefore conceivable that melatonin secretion is hampered in narcolepsy. Here we describe a study in which hourly melatonin levels are compared between narcolepsy patients and controls.

Part II Metabolic studies in narcolepsy

Hypocretins have a major role in glucose sensing and homeostasis[78] and therefore it is conceivable that hypocretin deficiency may lead to problems in glucose regulation and diabetes. Conflicting reports on the risk of diabetes in narcolepsy have been published. Several studies reported a higher prevalence of type 2 diabetes in narcolepsy.[22;39;41;95] More recent studies reported no difference in diabetes prevalence between narcolepsy patients and matched controls.[42;96] In chapter 6 we describe the first study to compare insulin sensitivity in nine narcolepsy with cataplexy patients compared with matched healthy controls, measured with the gold standard, the hyperinsulinemic euglycemic clamp technique. In addition, the effect of long term sodium oxybate treatment on insulin sensitivity is evaluated.

Sleep onset is preceded by an increase in skin temperature and a decline in core body temperature.[97] An altered thermoregulatory profile, resembling this sleep promoting pattern, has been observed in narcolepsy patients.[23] SXB is the sodium salt of GHB and may have

a positive effect on the sleep disturbances in narcolepsy.[73] The effect of both compounds are the same but the exact mechanisms are still unclear.[98] Altered thermoregulation is one of the effects of GHB described in animal studies and human case reports. Rodent studies demonstrate a slight increase in core body temperature after administration of a low dose of GHB and a clear decrease in core body temperature in higher doses.[99] In addition several studies describe hypothermia in humans with GHB intoxication.[100;101] Given the impact of GHB on temperature regulation, the altered pattern of skin temperature in narcolepsy and the positive effects of SXB on sleep in narcolepsy patients, the treatment effect of SXB may be, at least in part, mediated by restoring the physiological temperature regulation. Chapter 7 aims to determine the effect of short term Sodium Oxybate administration on the 24-hour temperature and sleep-wake profile in narcolepsy patients and controls.

Part III Other aspects of narcolepsy

Hypnagogic hallucinations are frequently described dream related experiences in narcolepsy. Confusions between dreams and reality are an often heard issue in narcolepsy, however so far no systematic studies have been published about these confusions. Here we describe an explorative study on delusional confusion of dreaming and reality in narcolepsy (chapter 8).

There are strong indications for an autoimmune cause of narcolepsy but there is no definite proof yet. One way to demonstrate an autoimmune cause involves studying the distribution of births over the months of the year. Several studies have addressed seasonal birth patterns in narcolepsy, suggesting an autoimmune involvement. Analysis methods in published studies varied, but no study corrected completely for possible changes in seasonal birth pattern over time in the appropriate control population. Therefore we describe the distribution of births over the months of the year of 307 narcolepsy patients compared to the general population in The Netherlands taking geographical and temporal criteria fully into account (chapter 9).