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NEUROLOGICAL UPDATE

Update on narcolepsy

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Abstract
The last two decades have seen an explosion in our understanding of the clinical nature of narcolepsy and its pathogenesis, fuelling new approaches to potentially effective treatments. It is now recognised that the full narcoleptic syndrome has significant adverse effects on sleep regulation across the full 24-h period and is often associated with clinical features outside the sleep–wake domain. The discovery that most narcoleptic subjects specifically lack a hypothalamic neuropeptide (hypocretin, also called orexin) was a truly original and landmark observation in 1999, greatly furthering our understanding both of the syndrome itself and sleep biology in general. An autoimmune pathophysiology has long been suggested by the tight association with specific histocompatibility antigens and very recently partly confirmed by detailed analysis of T-cell immunological function in affected subjects. Drug treatments remain symptomatic but may soon become more focussed by restoring central hypocretin signalling with replacement therapy. Potentially disease-modifying, immunological approaches have yet to be studied systematically, although the interval between disease onset and development of the full clinical syndrome may be longer than previously appreciated, affording a realistic window of opportunity for limiting neuronal damage in this disabling condition.

Keywords Narcolepsy · Hypocretin · Cataplexy · Autoimmunity

Introduction

Although uncommon with an incidence of around 1 in 2000 in Caucasian populations [1, 2], narcolepsy nearly always has profound and potentially disabling effects on affected subjects, especially as over a half will develop symptoms before 16 years of age [3]. Furthermore, less severely affected cases are frequently unrecognised, partly due to the relatively low profile of sleep medicine in training programmes. Delayed diagnosis often significantly hinders individuals achieving their full potential and diminishes quality of life [3]. Unfortunately, even on optimal conventional treatment, it is rare to fully "normalise" the sleep–wake cycle of narcoleptic subjects.

Following the landmark discovery in 1999 that familial canine narcolepsy was due to a mutation in the newly discovered hypocretin (type 2) receptor gene [4], it was soon established that typical human narcolepsy most often results from highly specific destruction of around 60,000 hypocretin-containing neurons in the lateral hypothalamus producing hypocretin deficiency [5]. This small collection of excitatory neurons projects to a wide range of targets including all the major wake-promoting nuclei in the brain, many limbic areas, as well as neighbouring parts of the hypothalamus [6]. Neurons containing hypocretin (also called orexin) are thought to integrate a variety of basic functions related to motivation and visceral needs, especially hunger [7, 8], keeping an organism fully awake for important events. Indeed, hypocretin activation leads to enhancement of arousal and autonomic tone, especially when seeking or expecting food and other primary goals or when responding to threat. Although of most interest to sleep researchers and clinicians, the neurobiology of hypocretin has attracted increasing attention in disparate areas of neuroscience, including the study of addiction. Genetic manipulations of the hypocretin system have led to a number of useful and valid rodent models of narcolepsy [9]. As a result, although the ultimate goal of preventing or limiting neural damage in human narcolepsy probably remains distant, effective treatment strategies to replace the deficient neuropeptide are close to clinical development.

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Clinical features

Narcolepsy is now best viewed as primarily a disorder of sleep regulation such that a subject is unable to easily maintain a stable state of wakefulness or, indeed, sleep for more than an hour or two. The REM sleep stage is particularly affected and elements of it, including paralysis and hallucinatory phenomena, readily intrude into wakefulness, especially when drowsy. Increasingly, it is appreciated that this "state instability" also applies to nocturnal sleep in narcolepsy which is almost invariably dysregulated and often frankly chaotic. Many subjects report significant sleep fragmentation and general motor restlessness during sleep. Indeed, the full range of parasomnias from both REM and non-REM sleep can be seen, as can frequent periodic limb movements. When present, it is uncertain to what extent features such as REM sleep behaviour disorder disturb sleep quality but attempts to improve sleep continuity may be fruitful and improve daytime functioning. At a practical level, most subjects find the cognitive and psychological sequelae associated with their symptoms of excessive sleepiness equally as disabling. Poor attention and memory causing "brain fog", reduced motivation, and secondary low mood are extremely common.

The highly specific phenomenon of cataplexy varies greatly between subjects and is sometimes the most troublesome aspect of the narcoleptic syndrome. Episodes generally start with weakness in the neck or facial muscles before descending paralysis of voluntary muscles over a few seconds in the context of an emotional stimulus, usually of a positive nature such as laughter. Weakness can be focal or partial and sometimes has a stuttering onset causing minor jerking, typically of the head. Particularly in children, partial facial weakness during episodes produces grimacing or tongue protrusion which can lead to diagnostic confusion, mimicking tics or even dystonia [10]. The precise neurobiological mechanism or neural circuit by which emotion or its anticipation triggers partial or complete REM sleep paralysis with retained awareness remains obscure, although activation of pathways from the amygdala to brainstem REM centres is thought to be central [11] (Fig. 1). In hypocretin deficiency, it is likely that activity in the pathway normally inhibiting REM sleep paralysis during wakefulness is silent,

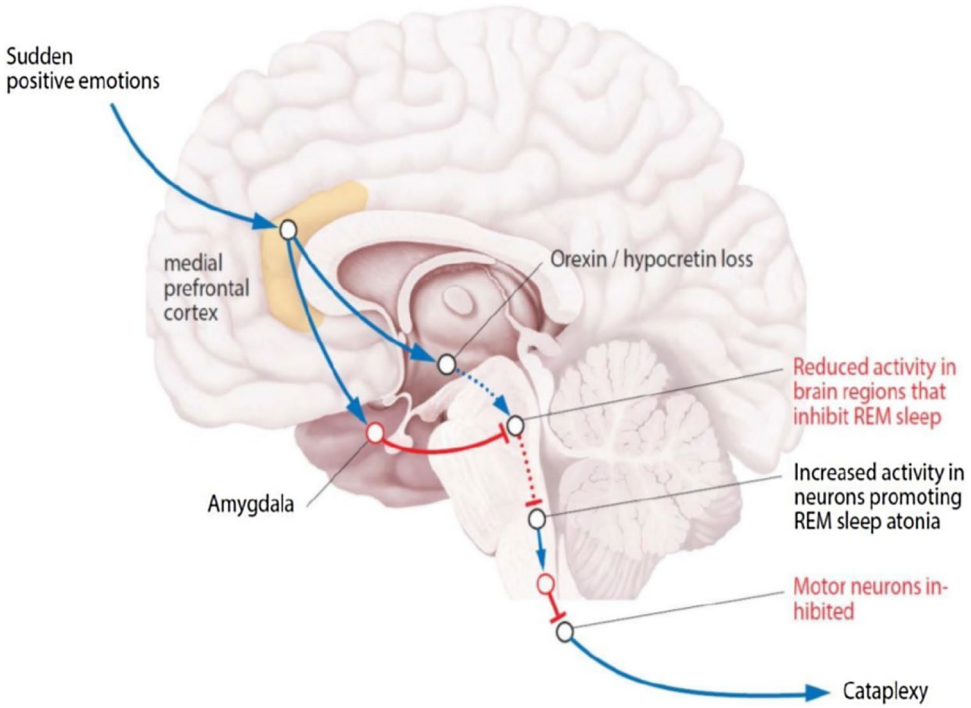

Fig. 1 Blue lines indicate activation of a neural pathway; red lines an inhibitory pathway. Dotted lines reflect lack of normal neural activity resulting from hypocretin deficiency in NT1. Based largely on functional imaging studies in narcoleptic subjects compared to controls, there is a proposed circuitry explaining cataplexy. Positive emotions such as humour are processed in medial prefrontal cortex with subsequent activation of both amygdala and hypocretin-containing neurons within the lateral hypothalamus. In the absence of hypocretin neurons, an imbalance is created such that a "REM-off" centre within the dorsal pons is inhibited. This, in turn, disinhibits the REM-atonia nucleus just beneath the locus coeruleus, the centre for producing the normal muscle paralysis in REM sleep. An activated descending pathway containing glycinergic neurons then actively inhibits voluntary motor neurons. This model is certainly oversimplified given that the mesolimbic ("reward") pathway is almost certainly also involved either at the level of the ventral tegmental area or ventral striatum

allowing the descending paralysis pathway to be activated. Intriguingly, this may reflect an exaggeration of a normal phenomenon and explains why a significant proportion of the population around the globe will occasionally describe "going weak with laughter" with possible diminution of peripheral H-reflexes [12].

A number of symptoms and medical issues not obviously or directly related to sleep are now recognised in narcolepsy and may well reflect other aspects of reduced hypocretin signalling. Many patients have dysregulation of appetite control and admit to severe food cravings, usually at night and particularly for sweet-flavoured items [13, 14]. Not infrequently, nocturnal eating occurs without conscious control or full awareness as an apparent non-REM sleep parasomnia that may accompany narcolepsy. As a possible consequence of disordered appetite control, rather than reflecting relative physical inactivity, obesity is significantly commoner in narcoleptic populations even though evidence suggests they eat less per day than control populations [15, 16]. Of note, soon after symptom onset around puberty, children typically and rapidly gain 5–15 kg in weight [17]. Whether this reflects a metabolic disorder, perhaps related to abnormal control of hypothalamic satiety or hunger hormones such as leptin or ghrelin, remains to be established. Similarly, although poorly studied, narcoleptic subjects also often report marked post-prandial sleepiness, particularly after large unrefined carbohydrate meals. Anecdotally, manipulations of diet, particularly limiting carbohydrates, can sometimes help to improve general alertness.

In animal models of hypocretin deficiency, drug-seeking behaviour is reduced for a variety of substances, including cocaine, opiates and alcohol [18–20]. Whether subjects with NT1 respond differently to reward or its anticipation is debated, although it is a common observation that psychostimulants used in narcolepsy very rarely produce euphoria or lead to addictive drug-seeking behaviours. If reward processing is indeed adversely affected, this might partly explain the twofold increased incidence of depression in narcolepsy [21, 22].

Clinical classification

The current classification of narcolepsy [23] recognises types 1 and 2 (NT1 and NT2) and relies either on objective testing of sleepiness or hypocretin levels (Table 1). NT1 reflects the classical clinical syndrome with excessive sleepiness and cataplexy as dominant features due to a measurable absence or severe deficiency of hypocretin in spinal fluid samples. NT2 is generally less severe and comprises a more nebulous, possibly heterogeneous entity. Excessive sleepiness occurs in NT2, usually with REM sleep-related problems such as abnormal dreaming or sleep paralysis but in the absence of cataplexy. The neuropathology of NT2

Table 1 New diagnostic criteria for narcolepsy from the third edition of the International Classification of Sleep Disorders (ICSD-3) [10]

Narcolepsy The subject must have periods during the daytime in which there is an irrepressible need to sleep or actual lapses into sleep, occurring for at least 3 months on a daily basis	
Type 1 narcolepsy	Type 2 narcolepsy
Narcolepsy with cataplexy and/or hypocretin deficiency	Narcolepsy without cataplexy
The presence of *one or both* of the following: Typical cataplexy and a mean sleep latency of ≤ 8 min with two or more sleep onset REM periods (SOREMPs) seen on a MSLT (i.e., REM sleep occurs within 15 min of sleep onset) performed according to standard techniques Note: a SOREMP on the preceding nocturnal PSG (i.e., REM onset within 15 min of sleep onset) may replace one of the SOREMPs on the MSLT. CSF hypocretin-1 concentration, measured by immunoreactivity, is less than 110 picograms/ml or < 1/3 of mean values obtained in normal subjects with the same standardised assay.	*All 4* of the following criteria must be met: A mean sleep latency of ≤ 8 min with two or more sleep onset REM periods (SOREMPs) seen on a MSLT performed according to standard techniques Note: a SOREMP (within 15 min of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT. Typical cataplexy is absent. Either the CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is > 110 picograms/ml or > 1/3 of mean values obtained in normal subjects with the same standardised assay. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnoea, delayed sleep phase disorder, or the effect of medication or substances, including their withdrawal.

The ICSD-3 classification now also recognises a pathophysiological subtype: narcolepsy type 2 due to a medical condition

All criteria are met for narcolepsy type 2 PLUS a disease likely to be responsible

Potential conditions included are: Parkinson's disease; myotonic dystrophy; tumours or infiltrative disorders such as sarcoidosis involving the hypothalamus; autoimmune or paraneoplastic conditions with auto-antibodies such as anti-Ma-2 or anti-aquaporin-4; multiple sclerosis; Prader–Willi syndrome; and head trauma

is usually unclear as cerebrospinal fluid (CSF) hypocretin levels are often normal, although a partial deficiency has been proposed. Rarely, narcolepsy is secondary to structural or inflammatory brain pathology involving the lateral hypothalamus seen on brain imaging [24]. Equally unusually, narcolepsy is found to run in families although cases are usually a little atypical and hypocretin levels are generally unremarkable [25]. The precise genetic abnormality in such cases is elusive, despite intensive interrogation of those genes responsible for producing hypocretin and its two receptors. Indeed, only one case of early onset narcolepsy due to a mutation causing impaired hypocretin trafficking has been discovered [26].

Pathophysiology

Even before it was established that NT1 is due to specific loss of a small number of hypothalamic neurons, an underlying (auto-)immunological mechanism was proposed, based on human leucocyte antigen (HLA) associations [27]. Indeed, for some time, NT1 has been known to have the tightest HLA link in any disease with the class II DQB1*06:02 allele conferring an increased risk of 200-fold. In those homozygous for this allele, the risk is doubled compared to that of heterozygotes [28]. Genome-wide association studies have identified other class II and some class I alleles as conferring risk or even protection for developing narcolepsy, although the effect sizes are considerably less than for DQB1*06:02 [29].

The notion of an autoimmune pathophysiology via molecular mimicry has been fuelled by anecdotal observations that NT1 can follow infections due to streptococci or respiratory winter viruses, including influenza. Of possible relevance, there is a robust seasonal peak of narcolepsy onset in late spring [30]. Furthermore, the well-publicised yet controversial association with the Pandemrix vaccine given as protection against swine 'flu (H1N1 virus) in 2009–2010 is thought to account for an 8–12- and 3–5-fold increases in new childhood and adult cases, respectively [31, 32]. Ascertainment bias may have played a role in explaining this surge in new cases although, of note, all were DQB1*06:02 positive and developed symptoms within a few months of inoculation. Whether the potential antigenic protein or peptide was from the viral nucleus or adjuvant material in the vaccine remains uncertain, although one recent study purports to have found molecular mimicry between the amidated terminal of hypocretin and a fragment of an H1N1 haemagglutinin protein [33]. Attempts to find clear evidence for pathogenic autoantibodies in narcoleptic subjects have generally been unrewarding and initial positive results have not been replicated [34, 35].

The mechanism of cell death in NT1 is most likely T-cell mediated with activated helper T cells ($CD4^+$) secreting cytokines and killer T cells ($CD8^+$) using cytotoxic granules to lyse target cells [36]. Activation of specific T-cell receptors (TCR's) is key to the process with recognition of antigenic-processed peptide fragments bound to classes I and II major histocompatibility complex (MHC) molecules. $CD4^+$ cells recognise antigens bound to class II molecules, potentially present on the surface of antigen-presenting glial cells, whereas $CD8^+$ cells respond to MHC class I–peptide complexes, generally not seen on neuronal surfaces. Of interest, crystalline modelling has indicated that a fragment of the hypocretin precursor protein (prepro-hypocretin) fits well in the binding groove of DQB1*06:02 [37]. Of equal interest was the finding that a single nucleotide polymorphism within the gene for the TCR alpha chain doubles the risk of NT1, speculatively by increasing the reactivity of T cells to hypocretin peptide fragments [38].

Using sophisticated immunological techniques, very recent research has identified the presence of $CD4^+$ memory T cells that recognise peptide antigens from hypocretin in all blood samples from a group of 19 narcoleptic patients [39]. In a control group of 13 subjects without narcolepsy, positivity was seen in three samples but this was of a low level and the proportion of reactive T cells was ten times less than in the narcoleptic group. The control group was pre-selected as being positive for the DQB1*06:02 allele which was also present in 14 of the narcoleptics. Although this provides strong evidence for autoimmunity, there were several puzzling aspects to the findings. The T cells were recognising hypocretin fragments attached to HLA proteins classified as HLA-DR as opposed to the expected HLA-DQ6 proteins encoded by DQB1*06:02. This might reflect a response shift in time over to HLA-DQ6 or the fact that the assessed T cells were from the bloodstream and may differ from those active in the brain. Also, the peptide fragments that triggered the T-cell response were not cleaved by antigen-presenting cells as might have been expected and were presumably generated extra-cellularly or within hypocretin neurons themselves. Furthermore, it was difficult to explain why two of the narcoleptic subjects with T-cell reactivity were not obviously hypocretin deficient (type NT2) as measured in CSF samples. Although these findings reflect an important breakthrough, it seems clear that the precise mechanisms and the sequence by which T-cell sub-types lead to hypocretin cell death remains somewhat speculative. It is possible that the reactive $CD4^+$ cells are present as a secondary consequence or that they reflect a "second wave" response after an initial primary immune attack. Of note, the authors did not find any cross-reactivity with antigens from the H1N1 influenza virus or the Pandemrix vaccine in contrast to the study by Luo and colleagues [33].

A number of case reports have documented progressive reductions in CSF hypocretin levels in subjects with atypical narcolepsy or NT2 that subsequently converts to NT1 [40, 41]. This would support the contention that an initial immune insult on the hypocretin neurons triggers a chronic inflammatory response or possibly a degenerative process that then progresses over months or even years. Speculatively, the latter may occur via an excitotoxic mechanism, given the extremely high metabolic demands of these particularly active neurons, especially if they are "overworked" after partial depletion.

Further insight into the potential increased vulnerability of hypocretin neurons with high energy demands is likely to come from further studies of a rare autosomal dominant disorder reported in several families with a DNMT1 point mutation [42]. Although the phenotype of affected individuals is very variable, particularly regarding symptom severity, many display typical features of NT1 with proven CSF hypocretin deficiency. Other clinical features such as deafness, neuropathy, ataxia, dementia and myoclonus usually dominate, however, and, intriguingly, closely mimic a primary mitochondrial disorder clinically.

Treatments

The vast majority of narcoleptic patients will benefit from pharmacotherapy, potentially alongside lifestyle changes. The first-line agent used for excessive daytime sleepiness is generally modafinil with more traditional psychostimulants such as dexamfetamine or methylphenidate as alternatives or add-on agents if the clinical response to modafinil is inadequate. If it is thought appropriate to treat REM sleep-related phenomena, notably cataplexy, drugs that generally suppress REM sleep are often effective. In practice, despite a paucity of controlled evidence, venlafaxine and clomipramine are most commonly used, typically at doses less than when prescribed as anti-depressants. Many narcoleptic subjects exhibit nocturnal sleep that is disturbed enough to merit therapy and considerable evidence suggests that sodium oxybate consolidates sleep, particularly by enhancing the deep or slow wave component [43]. This drug has also been shown to reduce cataplexy by up to 85% as well as improving daytime alertness [44]. It is a controversial agent, however, given its potential for misuse and high cost.

In 2016, a novel wake-promoting agent was approved for use in narcolepsy. Uniquely, Pitolisant acts as an inverse histamine receptor (type 3) agonist, effectively boosting hypothalamic levels of histamine and thereby enhancing wakefulness [45]. Its actions appear extremely specific and confined to the brain. It is also moderately effective for cataplexy and is generally very well tolerated [46]. A single dose of between 4.5 and 36 mg taken first thing in the morning is the usual schedule.

Another stimulant drug, Solriamfetol, has received approval as a wake-promoting agent in the USA [47]. It is thought to inhibit the re-uptake of noradrenaline and dopamine in a similar way to amphetamine-like agents, although the wake-promoting effects in narcolepsy appear novel. The trial data for use both in narcolepsy and treatment-resistant obstructive sleep apnoea appear promising, although it remains unclear how the drug's efficacy compares to existing wake-promoting therapies.

The exciting goal of replacing central levels of hypocretin using oral analogues may soon be a viable option given the promising animal research and early clinical trials in human patients [48, 49]. Previous attempts to restore hypocretin levels by a variety of routes and techniques have been unsuccessful, largely due to problems of drug delivery.

It is too early to predict whether immunotherapy, potentially by suppressing T-cell function with a specific monoclonal antibody, will be a worthwhile strategy, particularly in newly diagnosed narcolepsy. However, if the evidence favouring auto-immunity as the main pathophysiological mechanism becomes even more robust, such treatments are likely to be trialed.

Conclusions and future directions

There clearly remain numerous unanswered questions about narcolepsy particularly with regards to its variable clinical phenotype and underlying aetiology. The wide spectrum of symptom severity in subjects with equivalent undetectable CSF levels of hypocretin is unexplained and may reflect individual or differing compensatory neurochemical mechanisms utilised to overcome the effects of hypocretin deficiency. For example, although histaminergic levels in the CSF of NT1 subjects are generally low, there is considerable variation, implying that there are variable effects downstream of the hypocretin system that are likely to influence the overall clinical picture [50]. Hypocretinergic neurons also contain a variety of other transmitters such as excitatory glutamate, neuronal activity-regulated pentraxin (NARP), and inhibitory dynorphin [51–53]. The clinical effects of losing these transmitters remain speculative but probably explain the differing features between animal models with hypocretin deficiency due to cell loss compared to those with hypocretin receptor abnormalities [9]. Perhaps, even more puzzling is the entity of NT2 and whether this is a *forme fruste* of NT1 or a completely different disorder pathophysiologically, potentially reflecting several aetiologies. A major goal, therefore, is to refine our diagnostic parameters for NT2 and distinguish it from other primary sleep disorders such as idiopathic hypersomnolence.

As evidence supporting the auto-immune hypothesis of causation accrues, further identification of the relevant autoreactive T cells and associated antigens will be crucial for developing effective immunomodulatory treatments. If, as is likely, there is progression of neuronal loss in NT1, the window of opportunity for proactive immunological treatment may be wider than previously considered. In those subjects already lacking hypocretin, however, symptomatic treatment is likely to remain the main strategy and hypocretin analogues will almost certainly become a useful therapeutic option.

Compliance with ethical standards

Conflicts of interest The author has no conflicts of interest to declare.

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