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The neurobiology of hypocretins (orexins), narcolepsy and related therapeutic interventions

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Narcolepsy is characterized by excessive daytime sleepiness, cataplexy and other manifestations of dissociated rapid eye movement sleep. Narcolepsy is typically treated with amphetamine-like stimulants (sleepiness) and antidepressants (cataplexy). Newer compounds, such as modafinil (non-amphetamine wake-promoting compound for excessive daytime sleepiness) and sodium oxybate (short-acting sedative for fragmented nighttime sleep, cataplexy, excessive daytime sleepiness), are increasingly used. Recent discoveries indicate that the major pathophysiology of human narcolepsy is the loss of lateral hypothalamic neurons that produce the neuropeptide hypocretin (orexin). Approximately 90% of people diagnosed as having narcolepsy with cataplexy are hypocretin ligand deficient. This has led to the development of new diagnostic tests (cerebrospinal fluid hypocretin-1 measurements). Hypocretin receptor agonists are likely to be ideal therapeutic options for hypocretin-deficient narcolepsy but such compounds are still not available in humans.

What is narcolepsy?

Narcolepsy is characterized by excessive daytime sleepiness, disrupted nocturnal sleep, rapid eye movement (REM) sleep occurring at the onset of sleep, and cataplexy (a sudden progressive loss of skeletal muscle tone) in response to strong emotional stimuli (e.g. joking or laughing) [1]. The presence of cataplexy is distinctively characteristic for narcolepsy. Sleep paralysis (an inability to move, most commonly upon awakening) and hypnagogic hallucinations (dream-like events occurring at sleep onset) are also associated with the disease but these symptoms occur more variably.

These clinical characteristics of narcolepsy can be broadly placed into two categories: (i) an inability to consolidate wake and sleep (excessive daytime sleepiness, disrupted nighttime sleep) and (ii) dissociated REM sleep events (cataplexy, sleep-onset REM periods, hallucinations, sleep paralysis). Thus, unmedicated individuals with narcolepsy cannot stay awake for 16 consecutive hours per day, as is normal, and events that normally occur during REM sleep occur during the wake period of narcoleptics. It might be that, besides cataplexy, the other REM-related events that occur in narcolepsy are secondary, resulting from the disrupted sleep–wake pattern. In fact, sleep-onset REM periods, hallucinations and sleep paralysis have all been observed in individuals without narcolepsy but with severely disrupted sleep patterns (e.g. obstructive sleep apnea, circadian rhythm disorders and sleep deprivation) [2–4].

When narrowly defined by the presence of typical cataplexy, population-based studies have shown that narcolepsy affects approximately 1 in 2000 individuals in most countries [5]. Importantly, however, the prevalence of the milder form of narcolepsy, narcolepsy without cataplexy, could be substantially higher. Indeed, with the rapid growth in sleep medicine (i.e. recognition of diseases, number of practitioners and clinics, number of treatments available) [6], an increasing number of patients with daytime sleepiness not explained by sleep apnea or other causes, and exhibiting no cataplexy, are being recognized and treated symptomatically. Diagnosis for these entities involves the use of the multiple sleep latency test, a procedure in which sleep is recorded during brief daytime naps and sleep, and REM sleep occurrences at sleep onset are noted. These primary hypersomnias are now classified as narcolepsy without cataplexy (with sleep-onset REM periods) and idiopathic hypersomnia (without prominent REM sleep abnormalities) [1]. Importantly, however, the prevalence and pathophysiology underlying these conditions are not well understood (see below).

Neurobiology of sleep and narcolepsy

Sleep and wakefulness are controlled by a complex network of neurotransmitters and neuromodulators, such as glutamate, GABA, glycine, 5-hydroxytryptamine (5-HT), dopamine (DA), noradrenaline (NA), histamine (HA), acetylcholine, adenosine, neuropeptides, cytokines and prostaglandins (reviewed more completely in Refs [7,8]). A classic model presented in the 1970s focused on the interaction of monoamine and acetylcholine systems in the brainstem (i.e. the so-called ascending reticular formation). Much of this model rested on early transection experiments in cats that demonstrated a major role for the

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pontine brainstem in REM sleep generation. In this model, pontine monoamine tone is high during wakefulness, decreases in sleep and is almost absent in REM sleep. Acetylcholine tone is high during wakefulness and in REM sleep. High monoamine and acetylcholine tone during wakefulness contributes to electroencephalographic desynchronization both directly (via cortical projections) and indirectly (through thalamic projections). Electroencephalographic synchronization during REM sleep is mostly the result of increased acetylcholine tone. Of note, changes that are more variable have been reported for midbrain DA activity across the sleep cycle, possibly because these cells are more heterogeneous behaviorally, and across neuroanatomical subsets. More recently, however, sleep has been shown to involve an increasing number of cell groups and systems extending into the hypothalamus and basal forebrain, with descending projections in the spinal cord.

The importance of descending projections might be most evident during REM sleep, when there is an active inhibition of skeletal muscles via the medulla and spinal cord, resulting in complete atonia of antigravity muscles. GABA- and glycine-containing interneurons could be central to this mechanism. It has been hypothesized that the cataplexy observed in narcolepsy might be an aberrant activation of this inhibitory pathway during wakefulness, a 'breakthrough REM event' [9]. This activation might be induced either by disinhibition of the pathway that inhibits muscle tonus or by disfacilitation of the pathway maintaining muscle tonus but the exact mechanisms and pathways for induction of cataplexy are unknown.

Although the classic neuromodulators associated with sleep and wakefulness have brainstem origins, it has been known since the early 20th century, owing to the pioneering neuropathology work on encephalitis lethargica by von Economo, that the hypothalamus has both wake- and sleep-stimulatory areas as well [10]. von Economo noted that posterior hypothalamic and midbrain junction lesions resulted in sleepiness, whereas anterior hypothalamic inflammation resulted in insomnia. Almost 60 years later, it was recognized that one of these wake-stimulating posterior hypothalamic groups is the tuberomammillary histamine neurons [11,12]. Similarly to NA- and 5-HT-containing cells, histamine-containing cells are wake-active. The widespread use of histamine H_1 receptor antagonists, such as diphenhydramine, for mild insomnia is *prima facie* evidence for the importance of histamine in the regulation of sleep and wakefulness. Other experiments also indicate that the basal forebrain area, an area with wake-on acetylcholine-containing neurons, is another important sleep regulatory center.

Another wake-stimulating posterior hypothalamic group was discovered nearly simultaneously in 1998 by two groups [13,14]. This group is a small subset of neurons in the lateral hypothalamus that contains two neuropeptides, hypocretin-1 and -2 (also referred to as orexin A and B). Neurons producing these peptides (both encoded by the preprohypocretin gene) project widely to nearly all areas of the brain, notably innervating most nuclei involved in the regulation of sleep and wakefulness (Figure 1). There are two specific receptors for the hypocretin peptides, hypocretin receptor 1 and -2 (Hcrtr1, Hcrtr2), which have regional specificity and are part of the G-protein-coupled receptor superfamily [15]. A loss of hypocretin-producing neurons or of Hcrtr2 results in the sporadic and genetic, respectively, forms of narcolepsy in canines [16]. Using molecular biology to knock out the preprohypocretin gene or genetically targeting hypocretin neurons with a cell-specific toxin also causes a narcolepsy-like phenotype in mice [17,18]. Thus, animal data indicate that a loss of hypocretin neurotransmission might be associated with, or causal for, narcolepsy.

Confirming the animal data, the occurrence of narcolepsy in humans is often characterized by a loss of hypocretin neurons [19,20]. Clinically, this can be detected by abnormally low ($<$110 pg/mL) concentrations of hypocretin-1 in the cerebrospinal fluid (CSF) [21,22]. Hypocretin peptides are only found at significant concentrations in the CSF and brain tissue, with CSF hypocretin-1 being more stable and readily assayable than hypocretin-2, and are thus far not reliably detected in blood or other biological fluids [21,23]. Abnormally low CSF hypocretin-1 concentrations are found in approximately 90% of narcoleptics who also exhibit cataplexy. Large-scale genetic screens have failed to detect any hypocretin receptor mutations, even in several familial cases, and there has been only one documented case of narcolepsy due to a genetic defect of the preprohypocretin gene [19]. It is, therefore, most likely that in the smaller subset of individuals that have narcolepsy with cataplexy that is not associated with a loss or reduction in CSF hypocretin-1, the narcolepsy phenotype is due to defects downstream of the hypocretins. In addition to narcolepsy with cataplexy, narcoleptic patients can be diagnosed as having secondary narcolepsy or narcolepsy without cataplexy [1]. Secondary narcolepsy is due to a known neurological lesion (e.g. tumor, multiple sclerosis) and is often associated with a moderate reduction in CSF hypocretin-1 concentrations [22,24]. Narcolepsy without cataplexy is probably a pathophysiologically heterogeneous group because most ($>$75%) people diagnosed with narcolepsy without cataplexy have normal CSF hypocretin-1 concentrations [22].

Autoimmune mediation of narcolepsy

It has been hypothesized that narcolepsy might be an autoimmune disorder because it is sporadic in nature, there is low concordance between identical twins, it has a typical onset in the early twenties and, most importantly, 90–100% of all narcoleptics with cataplexy are positive for human leukocyte antigen (HLA) DQB1*0602 (c.f. 12–38% of the general population is positive for DQB1*0602) [25–28]. HLA class II molecules such as DQB1 are expressed on B cells, dendritic cells and activated T cells. These molecules are responsible for cell-to-cell recognition of self, and are therefore crucial components in the response to infection and in tissue rejection. There are several examples of HLA-associated autoimmune disorders, including rheumatoid arthritis, insulin-dependent diabetes mellitus and multiple sclerosis.

There has, however, been scant supportive biological evidence for an autoimmune response in narcolepsy. Antibodies directed towards hypocretin or hypocretin-

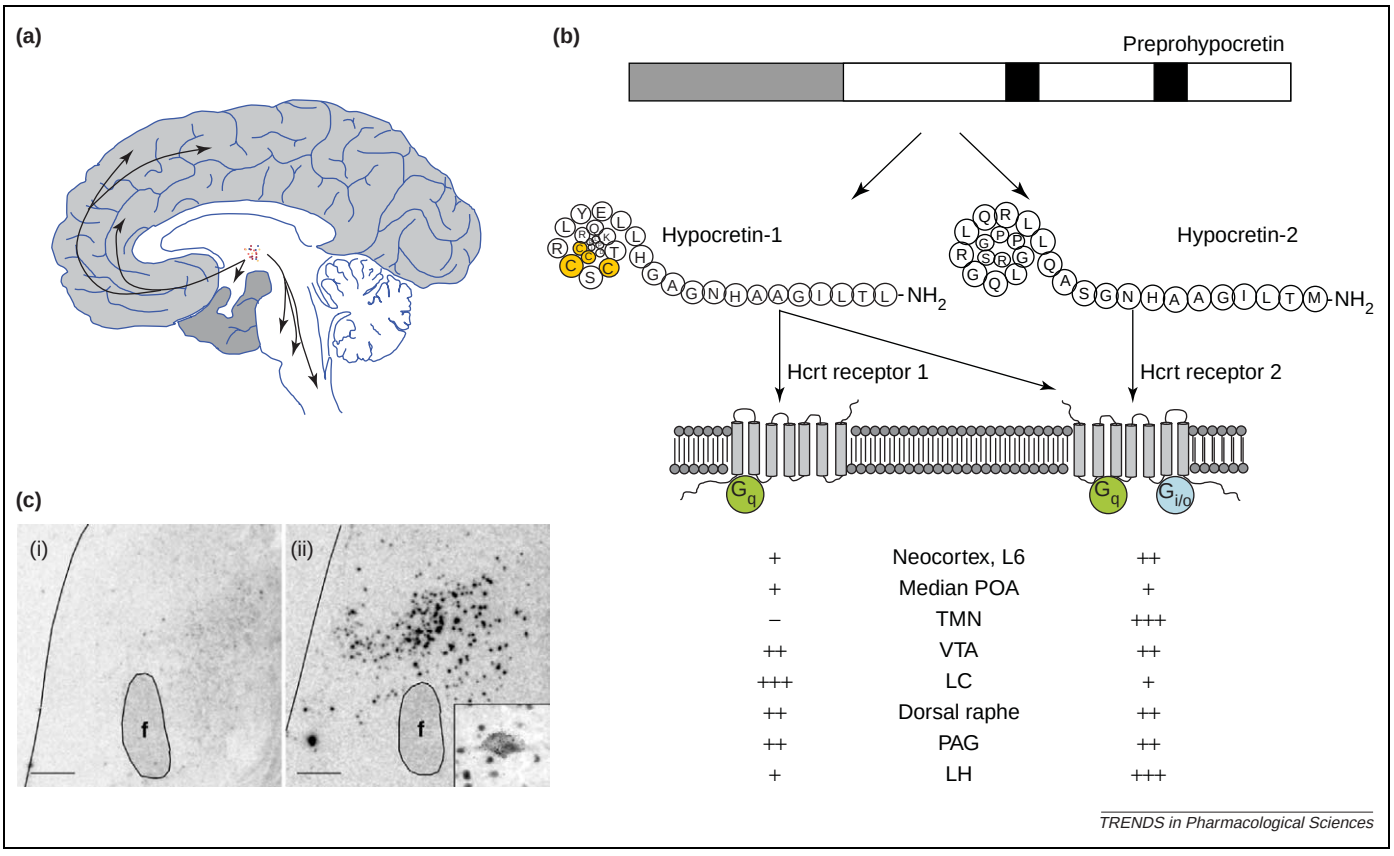

Figure 1. Anatomy of the hypocretin peptides and receptors. Hypocretin-containing neurons have widespread projections to most areas of the brain **(a,b)**. In (a) and **(c)**(ii), the neurons themselves are sparsely located in the lateral hypothalamus, and hypocretin staining is absent from the hypothalamus of people with narcolepsy (c)(i), as shown by *in situ* hybridization [17]. The distribution of the two hypocretin receptors, Hcrtr1 and Hcrtr2, is regionally specific (b) [12]. A subset of target areas is shown with relative density (+++=very dense) of the two receptor types. Hcrtr1 is more specific for hypocretin-1, whereas Hcrtr2 is equally specific for both hypocretins (b). Hypocretin-1 has a pair of disulfide bonds between cysteines (yellow) (b). It is not known whether the release pattern of hypocretin-1 and hypocretin-2 differs. Abbreviations: f, fornix; L6, cortical layer 6; LC, locus coeruleus; LH, lateral hypothalamus; PAG, periaqueductal gray; POA, preoptic area; TMN, tuberomammillary nucleus; VTA, ventral tegmental area. Scale bars in (c)=1 cm.

containing cells, or any other neuron- or organ-specific autoantibodies, have not been found and there has been no conclusive demonstration of autoimmune damage in the lateral hypothalamus of narcoleptics [19,20,29,30]. Gliosis has been observed in the brains of some narcoleptic patients [20] but these experiments were done from autopsied brains decades after any possible autoimmune attack, making interpretation difficult. Case reports of treatment with steroids and intravenous immunoglobulins near onset have also been controversial but might provide a partially effective therapy [31,32]. A potential explanation could come from animal models. Rats with a partial loss of hypocretin cells show no narcolepsy-like phenotype until at least a 30% loss of hypocretin neurons occurs [33], indicating that in humans, by the time of clinical presentation, the autoimmune attack might have progressed too far to be reversed by immune-based therapies.

Treatment of excessive daytime sleepiness

Current and recent treatments

Patients with narcolepsy are treated symptomatically. In the past, daytime sleepiness associated with narcolepsy was primarily treated with stimulants such as methylphenidate, dextroamphetamine or racemic mixtures of amphetamine. These compounds are structurally related (benzene core with an ethylamine group side chain) and share common pharmacological properties [24]. Amphetamine increases catecholamine (DA, NA) release and reduces reuptake of these catecholamines from the synaptic cleft via inhibition of the specific DA transporter (DAT) and NA transporter (NAT). Low doses of amphetamines (1–5 mg/kg) can also cause a reversal of DAT and NAT, which results in an efflux of cytoplasmic DA and NA into the synapse (i.e. exchange diffusion). At higher doses, amphetamine also inhibits vesicular monoamine transporters, which are responsible for moving monoamines from the cytoplasm into intracellular vesicles. With these distinct mechanisms, amphetamines and amphetamine-like compounds increase the overall signal strength at the dopamine-containing and noradrenaline-containing synapse [24] (Table 1). Although most pharmacological evidence indicates that enhancement of DA more than NA is crucial for mediating the wake-promoting effects of amphetamines, the physiological importance of DA in regulating wakefulness *per se* is unknown. Although amphetamine abuse is rare in narcoleptic patients with cataplexy, amphetamines can induce various sympathetic side effects as well as paradoxical rebound sleepiness [34] (Table 1). It is also advisable to use these compounds more carefully in cases without cataplexy because abuse potential can be more common in this population. Recent animal studies have suggested a role for hypocretin in

Table 1. Pharmacotherapy of narcolepsy[a]

Compound	Effect
Stimulants	
Amphetamine	Increases presynaptic monoamine release (DA > NA > > 5-HT). Increases DA release by reverse DA efflux through DAT. Minor inhibition of DA and NA reuptake, MAO activity and monoamine storage through the VMAT. The *D*-isomer is more specific for DA transmission and is a better stimulant compound. Some effects on cataplexy (especially for the *L*-isomer) secondary to noradrenaline-mediated effects occur at higher doses
Methamphetamine	Profile similar to amphetamine but more lipophilic with increased central penetration, greater prefrontal effects
Methylphenidate	Blocks monoamine (DA > NA > > 5-HT) reuptake through inhibition of DAT or uptake channel. Available as racemic mixture or as pure *D*-isomer (greater binding efficiency) and in various time-release formulations
Pemoline	Increases DA release and blocks DA reuptake. Little NA efficacy but low potency. Rarely used owing to occasional hepatotoxicity
Selegiline	(*L*-Deprenyl) MAO B inhibitor which is also converted *in vivo* into amphetamine and *N*-methylamphetamine
Modafinil[b]	Few peripheral side effects and lower addictive potential but also lower potency than amphetamine. Mode of action debated but probably involves DAT inhibition. Available as a racemic mixture; the *R*-isomer has a longer half-life and is in development
Anticataplectic compounds	
Clomipramine	Tricyclic antidepressant. Monoamine-reuptake blocker (5-HT > NA > > DA). Desmethylclomipramine is an active metabolite; it is an NA-uptake blocker with some 5-HT action. Anti-acetylcholine effects. All antidepressants have immediate effects on cataplexy but abrupt cessation of treatment can induce severe rebound in cataplexy
Desipramine	Tricyclic antidepressant. Monoamine-reuptake blocker (NA > > 5-HT > DA) with long-term desensitization of presynaptic alpha-2 and postsynaptic β-adrenoceptors. Anti-acetylcholine effects
Fluoxetine	Specific 5-HT-reuptake blocker (5-HT > > NA = DA). Minimal antihistamine and anti-acetylcholine effects. Active metabolite norfluoxetine has more adrenaline-mediated effects but is otherwise similar to parent compound. High therapeutic doses are often needed
Imipramine	Tricyclic antidepressant. Monoamine-reuptake blocker (NA = 5-HT > DA). Some D_1 DA receptor activity. Desipramine is an active metabolite. Anti-acetylcholine effects
Protriptyline	Tricyclic antidepressant. Mechanism of action not fully understood; likely to be a monoamine-reuptake blocker (NA > 5-HT > DA) with no MAO-inhibitory effects. Anti-acetylcholine effects
Venlafaxine[b]	Bicyclic antidepressant; specific 5-HT- and NA-reuptake blocker (5-HT ≥ NA > DA). Normally a racemic mixture, *D*-isomer is primarily a 5-HT-reuptake inhibitor and *L*-isomer is similar to racemate. Might have fewer sexual side effects than are seen for other antidepressants. Slightly stimulant, short half-life, extended-release formulation preferred
Atomoxetine[b]	Specific NA-reuptake blocker, normally indicated for attention-deficit–hyperactivity disorder and adult depression. Slightly stimulant, short half-life
Other	
GHB (also known as sodium oxybate)[b]	Might act via $GABA_B$ or specific GHB receptors. Reduces DA release at night, likely to cause secondary DA increase during day. Need bi-nightly dosing with immediate effects on disturbed nocturnal sleep; therapeutic effects on cataplexy and daytime sleepiness often delayed

[a]Abbreviations: MAO, monoamine oxidase; VMAT, vesicular monoamine transporter.
[b]These drugs are considered first-line treatment in narcolepsy with cataplexy.

modulating the abuse potential of stimulants and opioids. This might explain the relatively low abuse reported with these compounds in hypocretin-deficient narcolepsy cases with cataplexy.

The sleepiness of narcolepsy is now more often treated with modafinil, a new wake-promoting compound structurally unrelated to amphetamines. The mode of action of modafinil is controversial but it is thought to work by increasing dopamine tone via inhibition of DAT [35,36]. Modafinil is typically regarded as a better first-line drug in the treatment of the daytime sleepiness associated with narcolepsy because it does not have the sympathetic side effects and abuse potential associated with the older stimulants. It should be noted that amphetamine and modafinil promote wakefulness in both normal and hypocretin-deficit narcolepsy, in humans and animal models, suggesting that the sites of action of these compound are downstream or independent from the hypocretin system.

Neurobiological underpinnings of the excessive daytime sleepiness of narcolepsy

Both daytime sleepiness and nocturnal sleep disruption are likely to be due to an inadequate ability of narcoleptics to consolidate sleep and wakefulness. Normally, sleep and wakefulness are consolidated into eight- and 16-hour periods, respectively. Individuals with narcolepsy get the same total daily amount of sleep but it is not consolidated into a single nocturnal period. Sleep studies in narcoleptic animals with a deficient hypocretin system clearly show that their sleep and wakefulness are highly fragmented (shorter sleep and wakefulness bouts and higher frequency of state transitions) [37]. Diurnal fluctuation of hypocretin-1 release has been observed in cisternal CSF and microdialysis perfusates in animals, with a gradual increase during active periods, a decline during resting periods and maintained elevation during forced wakefulness [38–40]. This slow accumulation and decline of hypocretin-1 resemble those in delta-wave power that parallel with sleep propensity [41]. Hypocretin-1 tonus might thus be involved in the wake consolidation process by opposing the homeostatic pressure for sleep, thereby enabling longer periods of wake consolidation [38].

Hypocretin as a therapy: pitfalls and promises

Because most human narcolepsy–cataplexy cases are caused by hypocretin deficiency, hypocretin replacement

therapy is, theoretically, the most promising therapeutic avenue. Experiments using hypocretin cell-ablated mice suggest that central administration of hypocretin-1 can reduce cataplexy and prolong wake time in these animals [42]. This indicates that, at least in this model, the loss of hypocretin peptide does not cause a permanent loss of ability to respond to hypocretin-1 in a physiologically meaningful manner, and that such a response can be generated without spatially-targeted drug application. However, this therapeutic option is limited because intravenous hypocretin-1 does not effectively penetrate to the CSF and shows little or no therapeutic effects [43]. Thus, a priority of further pharmacological research is to develop CSF-penetrating non-peptide hypocretin agonists. This could be possible because at least a dozen non-peptide agonists for G-protein-coupled receptors are currently under development (e.g. urotensin-II, thrombin, galanin). Several investigators have reported initial testing of hypocretin agonists [43–46] using binding and calcium mobilization assays in cell lines. They have found that the entire hypocretin sequence is not necessary for agonistic activity; the C-terminal half of both hypocretin-1 (15-33) and -2 (10-28) are crucial for biological activity and receptor selectivity (notably, L-leucine at residues 11, 14, 15 in hypocretin-2 increases selectivity for Hcrtr2 over Hcrtr1) [45]. These results also suggest the possibility of developing small-sized hypocretin peptide analogs that can be selective for Hcrtr1 or Hcrtr2.

Other targets for treating excessive daytime sleepiness of narcolepsy

The neural networks downstream of hypocretin that are responsible for increasing wakefulness are now being discovered and could be an important target for future pharmacotherapy (Table 2). One of the major outputs of the hypocretin system that is thought to be involved in the promotion of wakefulness is its activation of the histamine-containing tuberomammillary nucleus through Hcrt2 [47,48]. The histamine-containing tuberomammillary neurons are normally wake-active and most likely inhibited during sleep by the prominent inhibitory GABA-mediated and galanine-mediated inputs they receive from the sleep-active neurons in the ventrolateral preoptic area. Intracerebroventricular administration of hypocretin-1 normally causes increased wakefulness but this effect is diminished or abolished when histamine-mediated transmission is blocked [49]. Altered histamine content in the brain or CSF in Hcrtr2-mutated narcoleptic dogs and hypocretin ligand-deficient human narcolepsy has also been reported [48,50]. The future use of H_1 receptor agonists is unlikely owing to the lack of available CNS-penetrating compounds and significant peripheral side effects. Current industry interest is therefore mostly focused on the H_3 receptor, which is an inhibitory autoreceptor on histamine-containing neurons. When located presynaptically on other neurons, it also regulates the release of several transmitters in brain areas such as the substantia nigra, amygdala and cerebral cortex. Stimulation of this receptor is sedative, whereas antagonists promote wakefulness (or reduce deep sleep) in rodents and dogs [51,52]. Experiments in narcoleptic canines and mice have found anticataplectic and wake-promoting effects for H_3 antagonists and inverse agonists [52,53]. Several pharmaceutical companies are currently developing or clinically exploring the use of H_3 antagonists to promote wakefulness and cognition for various indications. Whether the promising results in animal models will also extend to humans and whether these compounds will have enough efficacy remains to be established.

Treatment of cataplexy

Cataplexy has been commonly treated with antidepressants. First-generation tricyclic antidepressants (e.g. imipramine, protriptyline, clomipramine) can potently reduce cataplexy and are still the most commonly used anticataplectic agents (Table 1). Similar to the situation observed in patients with depression, the use of tricyclic antidepressants in the treatment of cataplexy is also

Table 2. Potential future narcolepsy therapies[a]

Therapy	Characteristics
Non-hypocretin-based therapy	
Novel monoamine-reuptake inhibitors	Anatomically targeted DA (stimulant) and NA (anticataplexy) reuptake inhibitors to reduce side effects and abuse potential
Novel SWS enhancers	Novel $GABA_B$ agonists, such as longer-acting GHB analogs; $GABA_A$ subtype-specific compounds (e.g. gaboxadol) or GABA-reuptake inhibitors (e.g. tiagabine) might be effective
Histamine-mediated H_3 antagonists or inverse agonists	Blockade of histamine H_3 receptors effective on sleepiness and cataplexy in animal models [52,53]; increases histamine, DA and NA release; effects in humans still uncertain but multiple compounds available preclinically or in early human trials
Hypocretin-based therapy	
Hypocretin-1	Disappointing effects after intravenous, intracisternal and intranasal administration to date but extremely high doses could still be effective [65–67]; would be likely to be effective if it could be delivered intracerebroventricularly
Non-peptide agonists	Best possible hope, however, peptide receptor agonists are often difficult, if not impossible, to make
Hypocretin cell transplant	Could eventually provide a cure; results to date in other diseases are disappointing because of graft rejection, low survival rate of implant and lack of supply for graft availability, which might be alleviated with stem cell technology. Likely to be more than ten years away
Gene therapy	Promising in the future; potentially dangerous side effects; could be combined with cell-based therapies
Immune-based therapy	
Steroids	Ineffective thus far [32]; unlikely to be useful owing to late clinical presentation of cell loss
IVIg	Positive results thus far, although not curative [31,68]; generally safe but occasional life-threatening side effects
Plasmapheresis	Similar to IVIg but even fewer available data [69]; more invasive than IVIg

[a]Abbreviations: IVIg, intravenous immunoglobulin; SWS, slow-wave sleep.

hampered by a number of problems, notably the relatively poor side-effect profile. This is mostly the result of their anti-acetylcholine properties, leading to dry mouth and associated dental problems, tachycardia, urinary retention, constipation and blurred vision (Table 1). The newer antidepressants (e.g. fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram), although showing a greatly improved side-effect profile, have been viewed as clinically less effective than the tricyclic antidepressants [54,55]. Among these compounds, fluoxetine at the 20–60 mg dose is a viable alternative to tricyclic compounds, and it has a good side-effect profile (including inducing anorexia rather than weight gain, a significant advantage for some patients).

A series of pharmacological experiments clearly demonstrated that noradrenaline-mediated-reuptake inhibition is the key property involved in anticataplectic effects [56]. Some of the newest antidepressants are selective reuptake inhibitors of NA (e.g. atomoxetine, reboxetine) or 5-HT–NA (e.g. venlafaxine, milnacipran) and are effectively and commonly used to treat narcolepsy, even though relatively few controlled experiments on the efficacy of these new compounds as anticataplectics have been conducted [57,58].

Hypnotic treatment in narcolepsy

Another potential area of improvement might be in the use of novel sedative hypnotics in narcolepsy–cataplexy. As mentioned above, most narcolepsy cases have disturbed nocturnal sleep because the primary abnormality in narcolepsy is the inability to consolidate sleep or wakefulness for prolonged periods. Benzodiazepines have been used for nocturnal sleep disruption but the development of tolerance, paired with a generally low efficacy in narcolepsy, minimizes their use.

Gamma-hydroxybutyrate (GHB, also known as sodium oxybate) was recently approved by the US FDA for treatment of narcolepsy. GHB occurs naturally in the brain as a metabolite of GABA [59] and stimulates either endogenous GHB receptors or $GABA_B$ receptors [60]. When taken as a bi-nightly dose, it improves nocturnal sleep, reduces daytime cataplectic attacks and other manifestations of REM sleep and also improves daytime alertness [61,62]. Although improvements in nocturnal sleep disruption occur relatively quickly, anticataplectic effects appear 1–2 weeks after the initiation of the treatment. It has been hypothesized that GHB might be sedative at night by inhibiting DA release and that this inhibition causes a greater pool of DA for release during the daytime, which is wake-promoting [63], but the precise mechanisms of action of GHB on sleepiness and cataplexy are largely unknown. A significant problem with GHB is the nonmedical use of this compound to elicit an altered state of consciousness, which has important social and legal implications [60].

Currently studied or available GABA-mediated hypnotics with sleep-enhancing properties include gaboxadol, a GABA-mediated modulator with preferential effects on extrasynaptic GABA receptors containing the delta and alpha-4 subunits, and tiagabine, a GABA-reuptake inhibitor [64]. The existence of numerous other potential targets for hypnotics, such as $5\text{-}HT_{2A/C}$ antagonists, histamine H_1 receptor antagonists or H_3 receptor agonists, and ion channel blockers, together with the renewed interest of the pharmacological sector in hypnotic therapies, could also be beneficial to narcoleptic patients.

Future perspectives

Eventually, treatment of narcolepsy–cataplexy is likely to involve hypocretin cell transplant or gene therapy technology (Table 2). However, these therapies are many years away, and the efficacy of exogenously administered hypocretin analogs (i.e. non-peptide agonists) should first be established in humans. Meanwhile, more specific targeting of the hypocretin system or downstream effector mechanisms with increasingly refined pharmacological agents might be the best short-term solution for the symptomatic treatment of narcolepsy. These other treatments will also serve the needs of a growing number of patients who do not have cataplexy.

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