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Narcolepsy and the hypocretin system—where motion meets emotion

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SUMMARY

Narcolepsy is a neurological disorder that is characterized by excessive daytime sleepiness and cataplexy—a loss of muscle tone generally triggered by certain strong emotions with sudden onset. The underlying cause of most cases of human narcolepsy is a loss of neurons that produce hypocretin (Hcrt, also known as orexin). These cells normally serve to drive and synchronize the activity of monoaminergic and cholinergic cells. Sleepiness results from the reduced activity of monoaminergic, cholinergic and other cells that are normally activated by Hcrt neurons, as well as from the loss of Hcrt itself. Cataplexy is caused by an episodic loss of activity in noradrenergic cells that support muscle tone, and a linked activation of a medial medullary cell population that suppresses muscle tone. Current treatments for narcolepsy include stimulants to combat sleepiness and antidepressants to reduce cataplexy. Sodium oxybate produces both reductions in cataplexy and improved waking alertness. Future treatments are likely to include Hcrt or Hcrt agonists to reverse the underlying neurochemical deficit.

KEYWORDS immunology, major histocompatibility complex class II, narcolepsy, rapid eye movement sleep, sleep

REVIEW CRITERIA

PubMed was searched for articles published up to 1 February 2006. Search terms included "narcolepsy", "hypocretin" and "orexin". Relevant articles were retrieved and prioritized for inclusion in the review. References of retrieved articles were checked for additional material.

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INTRODUCTION

Narcolepsy is characterized by excessive daytime sleepiness, disrupted night-time sleep, cataplexy, sleep paralysis, hypnagogic hallucinations, and short latency from waking to rapid eye movement (REM) sleep initiation. The onset of narcolepsy is typically in the second or third decade of life. In most patients, sleepiness and cataplexy are the main complaints. Some patients classified as narcoleptic according to current sleep nosology[1] do not show cataplexy, and many experience this symptom only rarely. It remains to be determined whether most cases of excessive sleepiness without cataplexy that are not attributable to another cause result from the same underlying disease process as most cases of narcolepsy with cataplexy.

For the 120 years following the identification of narcolepsy by Westphal[2] and its naming by Gelineau,[3] the cause of narcolepsy was a mystery, and the disorder was often attributed to psychiatric causes. In 2000, however, two simultaneously published papers determined that most human narcolepsy was linked to a loss of hypothalamic cells containing hypocretin (Hcrt, also known as orexin).[4,5]

In this paper, we will describe the anatomy, physiology, neurochemistry and behavioral role of the Hcrt system. We will review recent discoveries linking loss of Hcrt neurons to the genesis of human narcolepsy. Finally, we will discuss the implications of these findings for the treatment of narcolepsy.

THE HYPOCRETIN SYSTEM

The Hcrt peptides were discovered in 1998.[6,7] Hcrt1, which contains 33 amino acids, and Hcrt2, which contains 28 amino acids, are both encoded by the preprohypocretin gene. There are two known receptors for Hcrt: Hcrt receptor 1 (Hcrtr1) responds with moderate selectivity to Hcrt1, whereas Hcrt receptor 2 (Hcrtr2) responds similarly to both Hcrt1 and Hcrt2.

Cells containing Hcrt or synthesizing Hcrt receptors are present in several peripheral tissues, but little is known about their functions in these tissues. In the brain, Hcrt somata are found only in the hypothalamus, particularly in its perifornical, dorsomedial and lateral portions.[5,8] Hcrt cells project widely throughout the brain, and generally have excitatory effects on their postsynaptic cells. Particularly notable are the projections of Hcrt cells to cholinergic and monoaminergic cells.[9] In normal animals, noradrenergic, serotonergic and histaminergic cells are all tonically active during waking, and cease activity simultaneously during sleep. Hcrt appears to make an important contribution to facilitating the synchronous activity of these cells in individuals who are awake.

Some Hcrt cells contain glutamate, but few, if any, contain γ-aminobutyric acid (GABA).[10] Hcrt does, however, stimulate the release of both glutamate and GABA from synaptic terminals in Hcrt axonal projection regions.[11] We have shown that potent excitatory effects of Hcrt microinjection on masseter and hypoglossal motor neurons can be entirely blocked by prior injection of glutamate antagonists.[12] Intravenous injection of Hcrt produces glutamate release in the amygdala, a region with substantial Hcrt innervation, but not in the cerebellum, a region with minimal Hcrt innervation.[13]

The identity of the circuits that inhibit Hcrt neurons remains unclear. Hcrt cells are not inhibited by Hcrt itself; in fact, locally applied Hcrt acts through glutamatergic interneurons to produce further excitation.[14] Norepinephrine, presumably originating in medullary regions rather than the locus coeruleus, was reported to inhibit Hcrt cells in *in vitro* studies of transgenic mice,[14] but this finding has been challenged by *in vitro* studies in rats.[15] Serotonin (5-hydroxytryptamine or 5-HT) has been shown to inhibit Hcrt cells, and GABA-mediated inhibition also occurs, although the ultimate source of GABA innervation of Hcrt cells is unknown.[15]

LOSS OF HYPOCRETIN-PRODUCING CELLS IN NARCOLEPSY

Normal human brains have approximately 70,000 Hcrt cells. In brains from people with narcolepsy, however, only 10% of the normal numbers of Hcrt cells are seen, on average.[5] This cell loss is reflected in a reduced level of Hcrt in the cerebrospinal fluid (CSF),[16] although some narcoleptics with all of the classic symptoms, including cataplexy and excessive daytime sleepiness, have normal levels of Hcrt in their CSF.[17] It is possible that symptoms in these patients might be caused by non-Hcrt-related mechanisms or by dysfunction of presynaptic mechanisms regulating Hcrt release. It is also possible that surviving cells might compensate for a partial loss of Hcrt cells.[18] Such compensation, the variability in Hcrt assay measurements, and the demonstrated sensitivity of Hcrt levels to behavioral activity (see below) might all obscure subtle deficits in Hcrt function that are responsible for sleepiness and cataplexy.[19] Most narcoleptic patients with cataplexy have greatly reduced Hcrt levels. Therefore, there is little diagnostic uncertainty when cataplexy is present. Patients with narcolepsy without cataplexy, who have short latency to REM sleep onset and other symptoms of narcolepsy, often have normal Hcrt levels; measurement of CSF Hcrt levels might not, therefore, definitively resolve their status. Nevertheless, assays of CSF Hcrt might be useful in cases where symptoms are poorly defined.

One of the two papers that first reported greatly reduced numbers of Hcrt cells in individuals with narcolepsy showed that gliosis was present in the areas of Hcrt cell loss, a finding that was elaborated upon in a subsequent publication.[5,20] These findings indicate that an inflammatory reaction may have accompanied the loss of Hcrt staining, which would imply that cell loss occurred.

Two studies have addressed the question of whether the loss of immunohistochemically identified Hcrt cells in human narcoleptics might be due to a cessation of Hcrt production in cells that normally synthesize these peptides, rather than cell death. If this were the case, the symptoms might be reversed by restarting Hcrt synthesis. Hcrt cells are known to contain a peptide called dynorphin and a pentraxin called NARP (neural activity-regulated pentraxin). Dynorphin is an opiate that is thought to dampen the brain's response to other opiates. *NARP* is an 'immediate-early' gene, the protein product of which can turn on the expression of other genes and is involved in the clustering of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate) glutamate receptors.[21,22] Studies were conducted to determine whether protein or gene expression levels for these substances were reduced to the same extent as those of Hcrt in hypothalamic

regions. It was found that the number of cells containing these substances was reduced by approximately 90% in individuals with narcolepsy, the same reduction that was seen in cells staining positive for Hcrt.[21,22] These findings further support the hypothesis that narcolepsy is caused by the degeneration of Hcrt cells rather than by abnormal function of these cells. The gliosis and the NARP and dynorphin findings greatly reduce the likelihood that Hcrt cells have merely developed abnormally, or that they are intact but have ceased production of the peptide in narcolepsy. The effects of loss of Hcrt-containing cells are likely to result not only from the loss of Hcrt, but also from the loss of co-release of NARP, dynorphin and glutamate, and the effects of these losses on the release of glutamate and GABA from adjacent axonal terminals.

Hcrt cell numbers probably fall below some critical level in the weeks or months immediately preceding symptom onset in most cases of idiopathic narcolepsy. A slow progression is possible, but in at least some cases it appears that the degenerative process progresses from initiation to symptom onset in a matter of days or weeks. Most notably, a well-documented case of narcolepsy with cataplexy immediately followed an anaphylactic response to an insect sting.[23] Patients with narcolepsy typically report that their sleepiness symptoms worsen over a period of six or more months after symptom onset. In most cases, there is no obvious indication of immune activation at disease onset. Several cases of narcolepsy following head injury involving the hypothalamus, or relieved by removal of hypothalamic tumors, are consistent with the loss or inactivation of Hcrt being the proximal cause of narcoleptic symptomatology.[24,25]

Immunological factors

Identical twins are in most cases discordant for narcolepsy.[26] Most narcoleptics, however, share a particular human leukocyte antigen (HLA) haplotype,[27] determined to be HLA DQB1*0602.[28] Several known autoimmune disorders are HLA-linked,[29] so this discovery immediately suggested that narcolepsy might be an autoimmune disorder. The prevalence of this haplotype in narcoleptics with cataplexy is approximately 95%, compared with 20–30% in the general population. No mutations have been found in this HLA region or in adjacent regions of the genome in patients with narcolepsy,[28] indicating that this HLA haplotype is a risk factor for narcolepsy rather than a cause of the disorder. An extensive search for mutations in the genes responsible for the synthesis of Hcrt and Hcrt receptors in potentially familial cases of narcolepsy revealed only one mutation in more than 74 cases studied; this mutation resulted in an impairment of Hcrt trafficking and processing.[4]

A possible scenario for the onset of most cases of HLA DQB1*0602-linked narcolepsy with cataplexy is one in which targeted destruction of Hcrt—and potentially other cells—occurs following presentation of an exogenous antigen to the immune system via DQB1*0602 MHC class II molecules, perhaps in response to a systemic infection (Figure 1). This MHC class II:antigen complex may mimic the shape of an epitope on Hcrt cells or the cells to which they connect. Activated lymphocytes—T cells and B cells—readily cross the blood–brain barrier; in this way, an immune response that begins in the periphery could develop into an autoimmune attack on the brain. The immune system might then eventually destroy brain Hcrt cells when these neurons or related structures become the target of a highly specific immune attack involving cytotoxic T lymphocytes, antibodies synthesized by B cells, or both. Antibodies generated in response to a non-self antigen might cross-react with a self antigen on Hcrt cells, and autoantibody binding to Hcrt cells might result in killing of these cells by natural killer (NK) cells or by complement-mediated lysis. In addition, autoreactive cytotoxic T lymphocytes that recognize Hcrt cells might become activated after either cross-presentation of a non-self antigen by DQB1*0602 MHC class II molecules, or epitope spreading as a result of initial damage by NK cells or complement-mediated lysis. The nature of any CNS antigen that might be mimicked by such an MHC class II:antigen complex remains unknown. Logical candidates include portions of Hcrtr1 or Hcrtr2, cell-surface proteins associated with these receptors, or some other protein linked to Hcrt synthesis or Hcrt-containing cell bodies. Evidence that gliosis in humans with narcolepsy is most intense in terminal regions containing Hcrtr2[20] indicates that this receptor, or an antigen associated with synaptic complexes containing Hcrtr2, might be a target for immune-mediated attack.

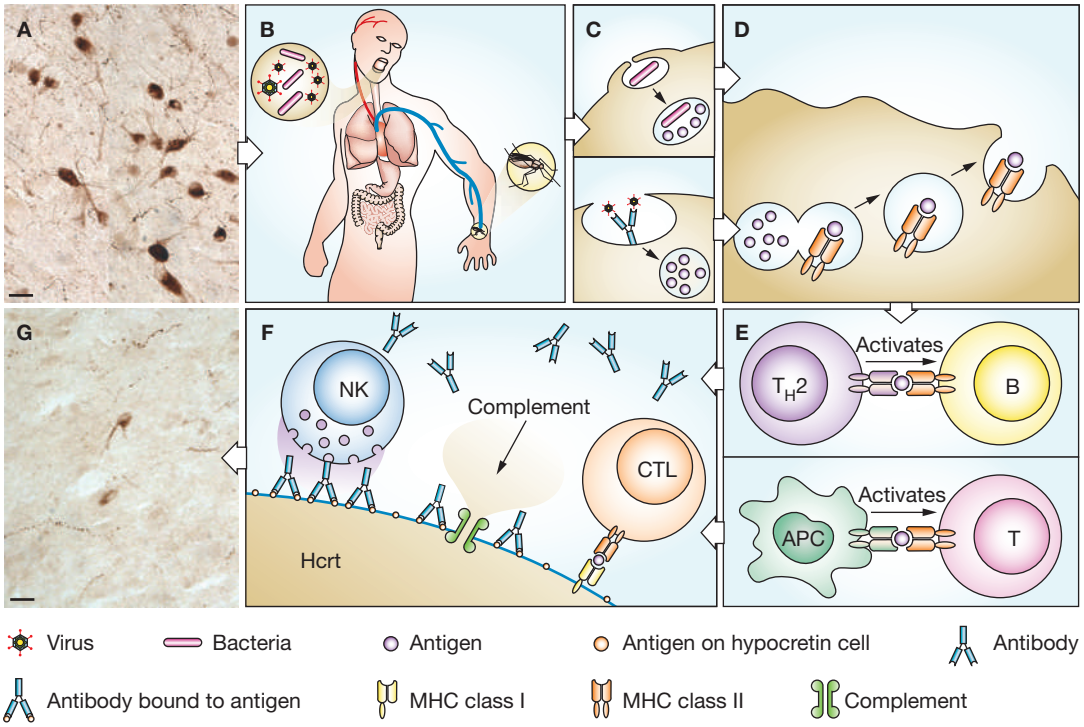

Figure 1 An autoimmune hypothesis of HLA DQB1*0602-linked narcolepsy with cataplexy. (**A**) Normal numbers of Hcrt cells are found in the non-narcoleptic human hypothalamus. Scale bar: 50 μm. (**B**) An individual is exposed to infectious agents and toxins through the respiratory and gastrointestinal tracts, and through direct contact with other tissues. (**C**) Top panel: bacteria, other pathogens and toxins are engulfed by phagocytic cells and broken down inside acidified endosomes. Bottom panel: viruses, other pathogens and toxins are bound by antibodies on B cells, endocytosed and digested in endosomes. (**D**) Vesicles containing newly synthesized HLA DQB1*0602 class II molecules pass through endosomes and bind peptide fragments. These MHC class II:antigen complexes are inserted into cell membranes on professional antigen-presenting cells, including macrophages, microglia, dendritic cells and B cells. (**E**) Top panel: a B cell presenting antigen via HLA DQB1*0602 class II molecules becomes activated by a helper T cell recognizing the MHC class II:antigen complex. The B cell proliferates, and large quantities of antibodies are produced. Bottom panel: a $CD4^+$ helper T cell, or possibly a cytotoxic T lymphocyte, becomes activated. (**F**) When the HLA DQB1*0602 class II:antigen complex closely resembles an epitope on Hcrt cells, these cells might be killed. Autoreactive cytotoxic T lymphocytes might kill cells. Antibody binding might also result in the killing of Hcrt cells by natural killer (NK) cells or complement-mediated lysis. (**G**) Few Hcrt cells remain in the narcoleptic human brain. Scale bar: 50 μm. Abbreviations: APC, antigen-presenting cell; B, B cell; CTL, cytotoxic T lymphocyte; Hcrt, hypocretin; MHC, major histocompatibility complex; NK, natural killer cell; T, T cell; T_H2, type 2 helper T cell.

Despite the evidence consistent with an autoimmune etiology of human narcolepsy, direct tests of this hypothesis that have looked for immune system activation and autoantibodies in narcolepsy have largely produced negative results. Several studies have looked unsuccessfully for the consistent presence of neuron-specific antibodies in narcolepsy.[30–32] Potential explanations for this lack of success include the possibility that the antibodies are only present at or near the time of symptom onset, and that the techniques used were not sufficiently sensitive to pick up evidence for autoantibodies. We cannot, however, rule out the possibility that autoimmune mechanisms do not underlie the loss of Hcrt neurons in narcolepsy.

Consequences of loss of hypocretin cell function

The loss of tonic Hcrt drive to histaminergic, dopaminergic, cholinergic and thalamic cells in awake individuals with narcolepsy makes it difficult to sustain waking periods, resulting in

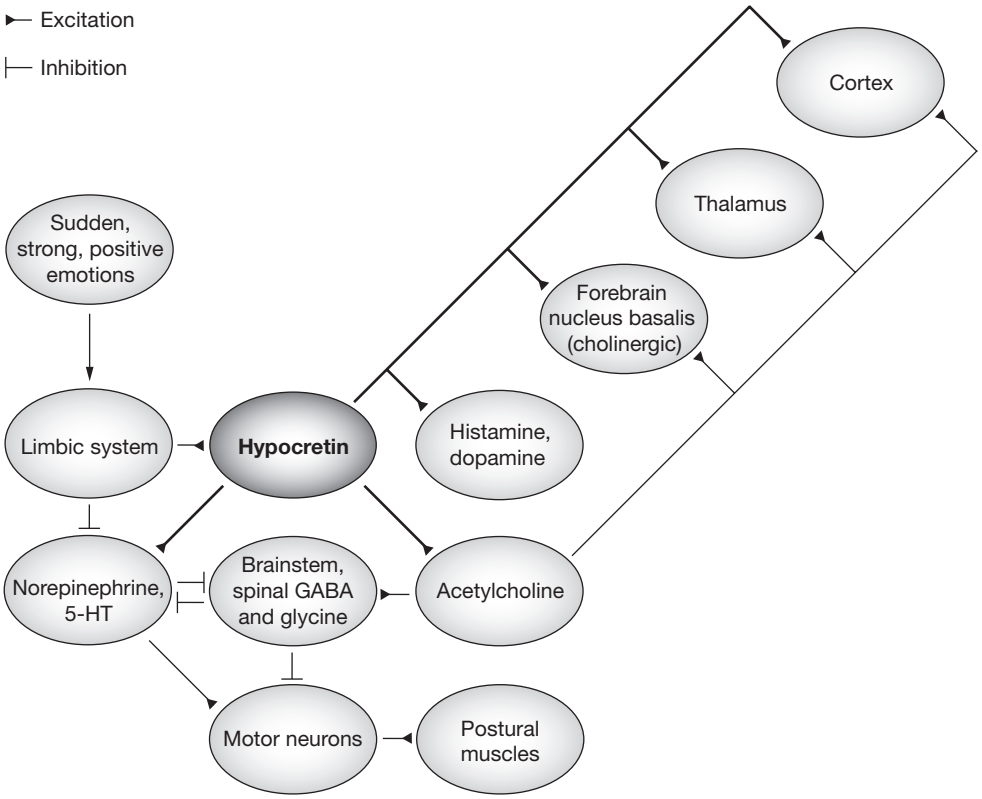

Figure 2 Hypothesized role of hypocretin (Hcrt) cells in the cataplexy and sleepiness of narcolepsy. Hcrt cell projections are shown in bold. Normally, the descending projections from Hcrt cells excite norepinephrine- and serotonin (5-hydroxytryptamine or 5-HT)-containing cells, which in turn excite motor neurons. Hcrt cells might also directly excite motor neurons. A phasic excitation of norepinephrine cells by Hcrt cells counters the phasic inhibition of norepinephrine cells mediated by the limbic system, typically in response to sudden strong positive emotions, such as laughter, the most common precipitant of cataplexy in humans. Norepinephrine and medullary inhibitory neurons discharge reciprocally, so that cessation of norepinephrine discharge is linked to increased activity in descending inhibitory systems. When the majority of Hcrt cells are destroyed in narcolepsy, the emotionally triggered inhibition of norepinephrine and 5-HT cells, coupled with the excitation of glycine- and GABA-containing cells in the medulla and spinal cord, reduces muscle tone, resulting in cataplexy. The ascending projections from Hcrt neurons directly and indirectly excite thalamic and cortical neurons, particularly through their action on histamine, dopamine neurons and acetylcholine neurons, thereby maintaining arousal. The loss of this influence results in the persistent sleepiness of narcolepsy. Abbreviations: 5-HT, 5-hydroxytryptamine; GABA, γ-aminobutyric acid.

sleepiness. In the absence of normal Hcrt function, norepinephrine-releasing cells can episodically cease discharge during waking hours, while histaminergic and serotonergic dorsal raphe cells remain active.[33] Normally, all three cell groups cease firing only during REM sleep. The loss of norepinephrine facilitation of motor neurons, and the synaptically linked increase in activity of brainstem GABAergic and glycinergic neurons that project to and inhibit motor neurons, results in the loss of muscle tone that constitutes cataplexy (Figure 2).[34,35]

BEHAVIORAL CORRELATES OF HYPOCRETIN RELEASE

We have monitored the release of Hcrt in a variety of behavioral situations. In one set of studies, we drew CSF from the cisterna magna of normal dogs. We found that, contrary to earlier ideas that Hcrt release is tightly coupled to food intake, there was little change in CSF Hcrt levels after 48 h of food deprivation or after meal ingestion, compared with CSF Hcrt levels under baseline conditions. By contrast, increased motor activity, caused by letting the dogs run in their

exercise yard, produced a near doubling of Hcrt level, compared with animals maintained awake in their normal housing.[19] In this situation, it is difficult to separate the effects of emotional excitement from motor activity.

Recently, we have developed techniques that allow us to record from identified Hcrt cells in freely moving rats. This allows us to achieve much better temporal resolution than is possible with CSF samples. We found that maximal Hcrt discharge is linked to exploratory behavior.[36] Lower levels of Hcrt cell activity are present during both grooming and eating, even when these activities are accompanied by higher levels of muscle activity than those seen when the animals explore. Furthermore, we have seen indications that situations that provoke anxiety can reduce discharge, even when high levels of motor activity and electroencephalogram activation are present. These emotional correlates of high or low levels of Hcrt activity are precisely those that are most likely to trigger or block cataplexy in rats in which genetic manipulations have rendered the Hcrt system nonfunctional.[37]

In narcoleptic dogs, cataplexy is triggered during vigorous play or eating of favored food, but not in aversive situations.[34] Similarly, in humans with narcolepsy, cataplexy most commonly occurs during behaviors accompanied by strong, positive emotions, with laughter being the most common trigger.[38] We have hypothesized that Hcrt cell activation counteracts the normal reduction in muscle tone that accompanies strong, positive emotions. We speak of "doubling over with laughter", but unlike patients with narcolepsy, normal individuals will not completely lose muscle tone and fall to the ground when they laugh. Hcrt activation of norepinephrine-containing cells might be the output pathway responsible for this muscle tone maintenance.[35]

The activity of Hcrt cells in rats is greatly reduced in non-REM sleep, and they are virtually silent during REM sleep.[36,39] The withdrawal of the excitatory influence of Hcrt might contribute to silencing of monoaminergic cells during sleep.[33] The absence of this coordinating influence in waking, together with a resulting increase in receptor sensitivity, might underlie the common and seemingly paradoxical (compared with cataplexy) disruption of muscle atonia seen during sleep in many individuals with narcolepsy.

TREATMENT OF NARCOLEPSY

Immunomodulatory treatment

The possibility that most cases of narcolepsy are autoimmune in etiology has led to several recent attempts to treat newly diagnosed narcolepsy by manipulating the immune system, with treatments including the use of steroids and intravenous immunoglobulin (IVIG).[40–42] Some symptomatic improvements have been noted; however, it remains unclear whether the symptomatic improvements are either reliable or long-lasting. A previous immunosuppressive and anti-inflammatory trial of the combination of methylprednisolone, methotrexate and azathioprine in genetically narcoleptic dogs produced dramatic reductions in symptom development.[43] In this case, the treatment could not have altered the underlying cause of the disease, which was a mutation in the *Hcrtr2* gene rather than the Hcrt cell loss seen in humans. Nevertheless, this work indicated that the immune system might be involved in the development and expression of the symptoms of genetic narcolepsy.

In humans, the trial treatments with immunosuppressant drugs did not significantly raise the reduced levels of CSF Hcrt. It is possible that a placebo effect is responsible for some of the observed improvement. It is also possible that immunosuppressive treatment could be causing symptomatic improvement in humans by affecting the function of brain systems linked to the symptoms of narcolepsy, including the monoaminergic and cholinergic systems. As short-term treatment had no effect on symptoms in genetically narcoleptic dogs, however, it would seem plausible that such treatments have immune-mediated or other effects on the disease process that we do not yet understand, rather than a direct pharmacological effect on symptoms.

Because most cases of narcolepsy are diagnosed after symptoms have fully or almost fully developed, manipulation of the immune system might not be a prudent approach to treatment, and pharmacological manipulation of other systems known to be involved might be more effective. Immunosuppressive treatments could have greater value if an assay were available to detect immunological changes or cell loss early in the degenerative process, rather than using the levels of Hcrt peptides in the CSF as is currently possible.

Hypocretin replacement

Despite the complexity of Hcrt anatomy and neurochemistry, there is evidence that Hcrt replacement therapy has the potential for reversing many of the symptoms of narcolepsy. It has been shown that Hcrt crosses the blood–brain barrier by diffusion.[44] We have shown that intravenous administration of Hcrt to narcoleptic dogs increases motor activity and decreases cataplexy,[45,46] and intracerebroventricular administration has similar effects.[46,47] An encouraging finding is that systemic administration did not produce obvious side effects, despite the presence of peripheral Hcrt and Hcrt receptors in the pituitary gland, testis, kidney, adrenal gland and gut.[48–51] Ectopic expression of Hcrt in a knock-in mouse model can 'rescue' mice that are narcoleptic owing to absence of Hcrt cells.[52] There is hope that treatment with Hcrt might be much more effective than conventional drug treatments in terms of increasing arousal, preventing cataplexy and ameliorating other symptoms associated with narcolepsy. Nevertheless, our neuronal recording studies reveal a very large modulation of Hcrt release in relation to waking behaviors, with certain waking behaviors being accompanied by little discharge, but other behaviors that occur a few seconds later being accompanied by maximal activity. Therefore, chronic systemic administration of the Hcrt peptide or transplantation of Hcrt cells is unlikely to substitute completely for the synaptically modulated release of Hcrt seen in normal individuals.

Preliminary attempts to administer Hcrt used intravenous and inhalation approaches.[53,54] Efforts are also being made to develop small-molecule Hcrt agonists that might be more cost-effective to produce and, importantly, might have a longer half-life than the native compounds. An alternative strategy might be to develop time-release formulations of Hcrt1.

Symptomatic treatment

In the absence of drugs based on Hcrt or Hcrt replacement, several pharmacological treatments for narcolepsy and its associated symptoms are available. One drug that is used to treat the persistent daytime sleepiness of narcolepsy is modafinil. The mechanism of action of this drug is unclear, but, like many stimulants, it might involve dopamine agonism or blockade of dopamine reuptake.[55] Early claims that modafinil might work through the Hcrt system were convincingly refuted in a study that showed greater wake-promoting effects of modafinil in *prepro-Hcrt* null mutant mice than in normal mice.[56] For many patients, modafinil treatment is not sufficient to sustain waking, and other stimulants, including methylphenidate, dextroamphetamine, methamphetamine and selegiline, are employed. In the future, thyrotropin-releasing hormone agonists[57] might prove to be useful. Direct histamine agonists have intolerable systemic side effects, but compounds that increase central histamine release, such as H_3 autoreceptor antagonists currently under development, might be effective arousal stimulating agents. In contrast to individuals with sleep apnea, narcoleptics find naps refreshing. In many patients able to adopt flexible schedules, periodic naps can reduce the need for, or substitute for, stimulant treatment.

In many patients, cataplexy has been effectively treated with tricyclic antidepressants and monoamine reuptake inhibitors, including selective 5-HT reuptake inhibitors. Such drugs include venlafaxine, atomoxetine, protryptyline, imipramine, desipramine, clomipramine, fluoxetine and reboxetine, all of which are thought to act, either directly or through their metabolites, on norepinephrine or 5-HT receptors. A newer treatment for cataplexy is sodium oxybate (gamma-hydroxybutyrate or GHB), which causes sustained, deep sleep. This drug is taken in two nightly doses, one at sleep onset and one in the middle of the night; benefits are felt nearly immediately, although several months are required to achieve maximal benefit. The mode of action remains unclear, but it is possible that GHB acts via $GABA_B$ or specific GHB receptors.[58] GHB is also effective against the sleepiness that characterizes narcolepsy.

CONCLUSIONS

We now have a greatly improved understanding of the physiological and neurochemical changes that characterize narcolepsy, and the Hcrt abnormality that underlies it. Future treatments for this disorder will undoubtedly employ Hcrt or Hcrt analogs. Such drugs might also have wider applications in the treatment of arousal and mood disorders.

KEY POINTS

- Narcolepsy is characterized by excessive daytime sleepiness, disrupted night-time sleep, cataplexy, sleep paralysis, hypnagogic hallucinations, and short latency from waking to the initiation of rapid eye movement sleep
- Cataplexy most commonly occurs during behaviors accompanied by strong, positive emotions, with laughter being the most common trigger
- In 2000, two simultaneously published papers determined that most human narcolepsy was linked to a loss of hypothalamic cells containing hypocretin (Hcrt, also known as orexin)
- In the brain, Hcrt somata are found only in the hypothalamus; Hcrt cells project widely throughout the brain, and generally have excitatory effects on their postsynaptic cells
- In brains from people with narcolepsy, only 10%, on average, of the normal numbers of Hcrt cells are seen; the loss of tonic Hcrt drive to histaminergic, dopaminergic, cholinergic and thalamic cells makes it difficult to sustain waking periods
- The possibility that most cases of narcolepsy are autoimmune in etiology has led to several recent attempts to treat newly diagnosed narcolepsy by manipulating the immune system
- There is evidence that Hcrt replacement therapy has the potential for reversing many of the symptoms of narcolepsy; several symptomatic treatments for narcolepsy are also available

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