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PHYSIOLOGICAL REVIEW

Neurobiological and immunogenetic aspects of narcolepsy: Implications for pharmacotherapy

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SUMMARY

Excessive daytime sleepiness (EDS) and cataplexy are common symptoms of narcolepsy, a sleep disorder associated with the loss of hypocretin/orexin (Hcrt) neurons. Although only a few drugs have received regulatory approval for narcolepsy to date, treatment involves diverse medications that affect multiple biochemical targets and neural circuits. Clinical trials have demonstrated efficacy for the following classes of drugs as narcolepsy treatments: alerting medications (amphetamine, methylphenidate, modafinil/armodafinil, solriamfetol [JZP-110]), antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors), sodium oxybate, and the H_3-receptor inverse agonist/antagonist pitolisant. Enhanced catecholamine availability and regulation of locus coeruleus (LC) norepinephrine (NE) neuron activity is likely central to the therapeutic activity of most of these compounds. LC NE neurons are integral to sleep/wake regulation and muscle tone; reduced excitatory input to the LC due to compromise of Hcrt/orexin neurons (likely due to autoimmune factors) results in LC NE dysregulation and contributes to narcolepsy/cataplexy symptoms. Agents that increase catecholamines and/or LC activity may mitigate EDS and cataplexy by elevating NE regulation of GABAergic inputs from the amygdala. Consequently, novel medications and treatment strategies aimed at preserving and/or modulating Hcrt/orexin–LC circuit integrity are warranted in narcolepsy/cataplexy.

Introduction

Approximately 1 in 2000 people are diagnosed with narcolepsy and more than 50% of patients report that their first symptoms occurred before 16 years of age [1]. Narcolepsy is characterized by excessive daytime sleepiness (EDS) and is classified as type 1 or 2 (NT1 and NT2, respectively) based on the presence or absence of cataplexy or hypocretin/orexin deficiency [2]. While the hypocretin (Hcrt)/orexin pathway has been established in the etiology of narcolepsy, translational neuroscience now provides evidence on how positive emotions promote cataplexy and how alerting medications used to treat EDS and cataplexy influence the underlying neural circuitry. The objectives of this manuscript are to review the clinical characteristics of narcolepsy, describe the neurophysiological, immunogenetic, and biochemical pathways involved in its etiology and symptomatology, provide an overview of current and novel therapies and their mechanisms of action, and to discuss future directions in the management of this disorder.

Clinical perspective

Narcolepsy is a neurological disorder of hypersomnia and its associated EDS and cataplexy are disabling to many patients. EDS is not specific to narcolepsy, occurring across a variety of disorders and can be due to loss of habitual nighttime sleep, sleep fragmentation, a circadian sleep-wake disorder, a primary neurological

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Abbreviations

α_2	Type 2 alpha adrenergic receptor
ACh	Acetylcholine
ADHD	Attention deficit hyperactive disorder
BLA	Basolateral area of amygdala
BMI	Body mass index
cAMP	Cyclic adenosine 3′,5′-monophosphate
CNS	Central nervous system
CeA	Central nucleus of the amygdala
CSF	Cerebrospinal fluid
DA	Dopamine
D_2	Type 2 DA receptor
DR	Dorsal raphe nucleus
EAA	Excitatory amino acid
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
FDA	United States Food and Drug Administration
GABA	Gamma-aminobutyric acid
$GABA_A$	Type 1 GABA receptor
GHB	Gamma-hydroxybutyrate
HA	Histamine
H_1	Type 1 HA receptor
H_2	Type 2 HA receptor
H_3	Type 3 HA receptor
Hcrt	Hypocretin
5-HT	Serotonin
$5\text{-}HT_{1A}$	Type 1A 5-HT receptor
HLA	Human Leucocyte Antigen
IVIg	Intravenous immunoglobulin
LC	Locus coeruleus
LDT/PPT	Laterodorsal tegmentum/pedunculopontine nuclei
LPT	Lateral pontine tegmentum
mPFC	Medial prefrontal cortex
MN	Motor neurons
MSL	Mean sleep latency
MSLT	Mean sleep latency test
MWT	Maintenance of Wakefulness Test
NE	Norepinephrine
NT1	Narcolepsy type 1
NT2	Narcolepsy type 2
OSA	Obstructive sleep apnea
PANDAS	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PET	Positron emission tomography
PGD_2	Prostaglandin D_2
REM	Rapid eye movement
SLD	Subdorsolateral tegmental nucleus
SNRI	Serotonin/norepinephrine reuptake inhibitor
SOREMP	Sleep-onset REM period
SSRI	Selective serotonin reuptake inhibitor
SubC	Nucleus subcoeruleus
SXB	Sodium oxybate
TCA	Tricyclic antidepressant
TRIB2	Tribbles homolog 2
vlPAG	Ventrolateral periaqueductal grey
VM	Ventromedial medulla
VTA	Ventral tegmental area

Glossary of terms

Attention deficit hyperactivity disorder (ADHD):
A psychiatric disorder characterized by an inability to focus, sustain attention, and modulate impulsive behaviors associated with impaired functioning and development.

Cataplexy: An emotionally-induced muscle atonia that manifests as limb, head, or facial weakness.

Excessive daytime sleepiness (EDS):
Persistent daytime sleepiness even after sustained nighttime sleep that is often associated with a lack of energy.

Human Leukocyte Antigen (HLA):
Cell surface proteins important in regulation of immune system function that are encoded by the major histocompatibility complex genes.

Hypocretin (Hcrt)/orexin:
A pair of neuropeptides, alternatively called hypocretin-1 (Hcrt1) and hypocretin-2 (Hcrt2) or orexin-A and orexin-B, that are synthesized within neurons located in the tuberal hypothalamus and contribute to the regulation of arousal, sleep-wake cycles, and energy metabolism.

Maintenance of Wakefulness Test (MWT):
A daytime polysomnographic proceedure that measures a person's ability to stay awake in a nonstimulating, dark and quiet room, for a determined period of time. This test provides an indication of excessive daytime sleepiness and alertness.

Multiple Sleep Latency Test (MSLT):
A test used to differentiate physical tiredness from excessive daytime sleepiness. It measures sleep latency which is the duration from the start of a daytime nap to the first sign of sleep using polysomnography.

Narcolepsy type 1 (NT1):
Narcolepsy type 1 is associated with low levels ($\leq$110 pg/mL), or the absence of, Hcrt1/orexin-A in the CSF. EDS and cataplexy (which is typically present) are often the phenotypic presentations along with REM sleep abnormalities.

Narcolepsy type 2 (NT2):
Narcolepsy type 2 is associated with CSF hypocretin-1/orexin-A levels $\geq$110 pg/mL. Cataplexy is absent. EDS with abnormalities of REM sleep is often the phenotypic presentation.

Obstructive sleep apnea (OSA):
Regarded as the most common sleep breathing disorder, OSA is characterized by a significant reduction or cessation in airflow during breathing effort. If excessive daytime sleepiness occurs from OSA, it is called obstructive sleep apnea syndrome.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS):
An autoimmune reaction caused by a streptococcus bacterial infection which impacts the basal ganglia and produces symptoms of obsessive-compulsive disorder, Tourette syndrome, and involuntary movements (i.e., tics).

Rapid eye movement (REM) sleep:
A period of sleep with rapid movements of the eye muscles, characteristic electroencephalogram (EEG) findings, physiologic changes such as increased heart and brain activity, and reduced muscle tone. Also called "paradoxical sleep" in animal studies, REM is linked to dreaming in humans.

Sleep onset REM periods (SOREMPs):
A period of REM sleep that occurs ≤ 15 min after sleep onset and measured using an overnight polysomnography (PSG). This test is applied to assist in making a diagnosis of narcolepsy.

disorder, or sedating drugs. In narcolepsy, sleepiness is characterized by a daily underlying irresistible drive for sleep that is associated with impaired cognitive ability, reduced psychosocial functioning and quality of life that puts patients at risk of work-related, home, or automobile accidents [2]. Narcolepsy also confers a substantial socioeconomic burden with nearly double utilization of healthcare resources, increased costs to employers due to work absence and short-term disability, and costs to patients with increased job loss and unemployment [3].

The cause of the sleepiness in narcolepsy, particularly patients classified as the NT1 subtype which is associated with cataplexy, is due to loss or severe reduction of the number of Hcrt cells in the hypothalamus. Hcrt deficiency decreases activation of the cortex, basal forebrain, hypothalamus, and brainstem by reducing excitation of neurons synthesizing wake-promoting neurotransmitters such as norepinephrine (NE), dopamine (DA), serotonin (5-HT), and histamine [4]. Hcrt-producing neurons stimulate brain regions that inhibit rapid eye movement (REM) sleep and extensive loss of Hcrt neurons causes dissociated REM sleep, the most dramatic manifestation of which is cataplexy [2,4].

Cataplexy is pathognomonic for narcolepsy. In a typical cataplectic attack, there is sudden, spontaneous, and bilateral loss of voluntary muscle tone. Symptoms range from slurred speech and drooping face to collapse to the ground for 1–2 min, leaving the patient unable to move yet fully conscious. The cause of sleepiness in NT2, a narcolepsy subtype that is not associated with cataplexy, is unclear but may be due to moderate Hcrt neuron loss or insufficient release of the Hcrt neuropeptides without detectable reduction in cerebral spinal fluid (CSF) Hcrt levels. In narcolepsy, considerable individual variation occurs in patient response to medications, likely reflecting that current medications are targeting symptoms rather than the cause of this disorder.

Clinical tests for narcolepsy exist but can produce false negative results which contribute to misdiagnosis [5]. The symptom of sleepiness in narcolepsy is often not recognized as due to a specific neurological disorder and can be erroneously attributed to attention deficit hyperactivity disorder (ADHD), particularly in children, or to obstructive sleep apnea (OSA) syndrome, insufficient sleep, idiopathic hypersomnia, or a psychiatric disorder in adults [1]. Only 18% of patients with narcolepsy receive a diagnosis within 1 year of symptom onset and only 50% of patients with narcolepsy receive a diagnosis within 5 years [1]. Furthermore, symptoms of narcolepsy are more likely to be missed if they develop before 18 years of age, with a diagnostic delay almost double to that of patients with first symptoms after 18 years [6]. EDS in children with narcolepsy can manifest as attention problems, behavior resembling hyperactivity, and emotional lability, leading to a misdiagnosis of ADHD [2]. Cataplexy in children with narcolepsy also tends to be atypical and contributes to misdiagnoses, given features such as cataplectic facies (i.e., jaw slackening, perioral movements, grimacing, and tongue protrusion), dyskinetic movements, and long-lasting periods of low muscle tone with gait instability [2].

Narcolepsy subtypes and diagnostics

Narcolepsy is currently classified into NT1 and NT2, with chronic daily sleepiness for ≥3 months needed to satisfy the diagnostic requirement [5]. The diagnostic criteria for NT1 in adults is largely based on the presence of cataplexy with reduction in CSF Hcrt1/orexin-A to <110 pg/mL [5]. Confirmation of this diagnosis involves polysomnographic testing indicating REM sleep onset of <15 min on nighttime sleep, a mean sleep latency time of ≤8 min on the multiple sleep latency test (MSLT), and two or more sleep onset REM periods (SOREMPs) [5,7]. The presence of SOREMPs are an important finding used to differentiate a diagnosis of narcolepsy from that of idiopathic hypersomnia and primary hypersomnias. A SOREMP on polysomnography occurs in approximately 50% of NT1 patients [8]. NT2 narcolepsy is diagnosed by the same polysomnographic criteria as NT1 but with the absence of cataplexy or a known CSF Hcrt1/orexin-A level <110 pg/mL.

Up to 60% of patients with narcolepsy have cataplexy (NT1). Cataplexy is usually triggered by positive emotions such as laughing, joking, or meeting a friend, and less frequently by negative emotions, including anger and frustration. Multiple lines of evidence suggest that cataplexy and REM sleep paralysis share common circuit mechanisms involving medial prefrontal cortex and amygdala pathways to the pons, resulting in decreased suppression of REM sleep secondary to Hcrt deficiency [2,9]. Approximately 10% of patients with NT2 will develop cataplexy; these are more likely to be individuals with Hcrt deficiency [2]. Rare patients with idiopathic hypersomnia have progresssed to features of NT2 and, ultimately, NT1, suggesting that some forms of idiopathic hypersomnia may have subtle Hcrt loss, whereas other forms may be related to GABA abnormalities [10,11]. Although true cataplexy occurs very rarely in disorders other than narcolepsy, namely Coffin-Lowry syndrome and Niemann-Pick disease Type C, syncope and epileptic phenomena can closely mimic cataplexy and need to be considered during diagnosis [5]. Furthermore, patients with narcolepsy often have medical comorbidities including OSA, diabetes, obesity, digestive problems, upper respiratory tract infections, heart disease, hypertension, and psychiatric disorders [9] requiring special consideration for medication. Obesity and increased body mass index (BMI), particularly at disease onset, may be linked to decreased metabolism secondary to Hcrt deficiency. OSA coexists in approximately 50% of patients with narcolepsy, which may be related to increased BMI in these patients [3]. Depression is common in narcolepsy and has been reported in 25–60% of patients; anxiety has also been reported to occur in 18% of patients, prompting recommendation for routine screening for psychiatric symptoms that are linked to Hcrt deficiency in patients with narcolepsy [12,13].

Genetic and immunological contributions to narcolepsy-cataplexy

Narcolepsy is considered to affect individuals with a genetic susceptibility that predisposes to immune system activation when

exposed to yet-unknown environmental stimuli. Monozygotic twins are 25–30% concordant for narcolepsy with cataplexy [14], a degree of concordance that supports both a genetic predisposition underlying narcolepsy as well as a role for environmental factors. Although only 1–2% of first - degree relatives share narcolepsy diagnoses, this represents a 10–40× increase in risk relative compared to the general population [14].

The primary genetic risk factors for narcolepsy identified to date are the genes that encode the major histocompatibility complex (MHC) proteins (i.e., the HLA genes). The HLA genes encode molecules that present antigen fragments to the T-cell receptor in order to direct an immune response to a specific antigen. Type 1 narcolepsy (NT1) is highly associated with HLA class II polymorphisms in the closely linked loci DQB1*06:02 and DQA1*01:02, which together form the DQ0602 heterodimer. Almost all patients with narcolepsy and cataplexy (82–99%) are carriers of DQB1*06:02 while only 12–38% of non-narcoleptic individuals carry this allele [14]. DQB1*06:02 is considered to be a susceptibility factor in the disorder; the susceptibility risk for narcolepsy is two-fold in individuals who are homozygous for DQB1*06:02 compared with heterozygous carriers. Conversely, DRB1*03-DQB1*02, DRB1*1301-DQB1*0603, DQB1*05:01, DQB1*06:09, and DQB1*02 are thought to be strongly protective for the development of narcolepsy in Europeans [15,16] and HLA-DPA1(*)01:03-DPB1(*)04:02 and HLA-DPA1(*)01:03-DPB1(*)04:01 are protective in Asian populations [17]. HLA class I alleles have also been reported to confer risk of, and protection from, narcolepsy [17]. Other predisposing factors for narcolepsy are associations with a polymorphism in the *T-cell receptor alpha* and *beta* genes, whose products recognize antigens presented by HLA molecules, and *Cathepsin H,* which processes antigens for presentation [18]. Rare missense mutations in the gene encoding purinergic receptor subtype P2RY11, expressed in cytotoxic lymphocytes as well as in the brain, have also been shown to be associated with narcolepsy and resulted in functional deficits in P2RY11 signalling through both the calcium ion and the cyclic adenosine 3′, 5′-monophosphate (cAMP) pathways [18]. The tight linkage between narcolepsy and HLA subtypes and other genes involved in autoimmunity such as *TNFSF4, IL10RB-INFAR1,* and *P2YR11/DNMT1* are consistent with a long-hypothesized autoimmune basis for this disorder [19].

Hypothesized autoimmunity

Although it is well established that NT1 is caused by neurodegeneration of Hcrt cells and a genetic component in immune function confers susceptibility to the disease, how these factors together contribute to the etiology of narcolepsy is unknown. The hypothesis that narcolepsy is an autoimmune disease that targets Hcrt neurons seems plausible, but the mechanism has remained elusive for decades [20]. Until very recently [24], autoantibodies against the Hcrt peptides, Hcrt receptors, or antigens co-localized on Hcrt neurons have evaded detection. The absence of identified autoantibodies in narcolepsy heretofore contrasted with other CNS autoimmune diseases, although some evidence for autoantibodies exists. Sera from a small group of patients with narcolepsy has been shown to bind tribbles homolog 2 (TRIB2), a protein kinase that has been linked to autoimmune uveitis. However, since TRIB2 is expressed in many tissues both in the CNS and in the periphery and not just in Hcrt neurons, TRIB2 autoantibodies are unlikely to be causative of Hcrt neurodegeneration and a recent study indicates that the anti-TRIB2 antibody in narcolepsy patients may be a consequence, rather than the cause, of Hcrt neuron degeneration [21].

As a test of the autoimmune hypothesis, sera obtained from patients with narcolepsy and patients with other sleep disorders were screened using rodent brain tissue. Three distinct patterns of immunoreactivity were observed, one of which was found to correspond to the C-terminal epitope of the neuropeptide glutamic acid–isoleucine/α-melanocyte-stimulating hormone [22]. However, CSF samples from NT1 patients collected within 1–12 months of narcolepsy onset did not exhibit any change in the 51 cytokines and chemokines examined when compared with healthy controls and, furthermore, failed to replicate the previously reported elevation of the cytokine interleukin 4 in this population [23].

Support for the autoimmune hypothesis has recently been obtained by the identification of hypocretin-specific $CD4^+$ T cells in the blood of both NT1 and NT2 patients, irrespective of whether the subjects were DQB1*06:02 positive or not [24]. The proportion of $CD4^+$ T cells that recognized Hcrt was more than 10-fold higher in individuals with narcolepsy than in controls. The $CD4^+$ T cells that recognized Hcrt did not cross-react with influenza antigens linked to the increased incidence of narcolepsy associated with the H1N1 virus (see below). Curiously, most $CD4^+$ T cells were restricted to HLA-DR and did not recognize Hcrt peptides bound to the HLA-DQ6 proteins which are encoded by DQB1*06:02. Since one NT2 patient had $CD8^+$ T cells that recognized Hcrt and subsequently developed cataplexy, one possibility is that circulating $CD8^+$ T cells may be an earlier indicator of ongoing neuronal destruction than are $CD4^+$ T cells [25]. A recent report indicates that the number of T cells that respond to Hcrt peptides presented by HLA-DQ6 is higher in patients with recent-onset narcolepsy [26]. These observations are of interest because a mouse model has been established in which $CD8^+$ T cells kill Hcrt neurons [27]. T cells in the bloodstream may have different HLA preference than those in the brain, an important consideration since hypothalamic neurons do not typically express Class II MHC molecules (e.g., HLA-DR and DQ) to which $CD4^+$ T cells bind but constitutively express the Class I MHC molecules that $CD8^+$ T cells recognize [28].

Infections can induce autoimmunity through a wide variety of mechanisms, including molecular mimicry, epitope spreading, bystander activation, and superantigens, with a growing body of evidence suggesting that pathogens can trigger narcolepsy [29]. Narcolepsy onset is more frequent in the spring and early summer than in the winter, perhaps triggered by upper airway infections during winter [30]. Streptococcal throat infection has been associated with a 5.4-fold increased risk of narcolepsy [31], and anti-streptococcal antibodies have been detected in 65% of patients with recent narcolepsy onset compared with age-matched controls [32]. Serum from children with Syndenham's chorea or pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) has been shown to contain cross-reactive antineuronal antibodies that can alter dopaminergic signaling pathways [33], but whether a similar cross-reactivity can affect the Hcrt system remains to be determined. Hcrt/orexin–specific $CD4^+$ T cell activation in human narcolepsy has not been corroborated [34], so how an immune response to the virus may ultimately cause Hcrt cell death remains to be determined.

Perhaps the most informative connection between narcolepsy and an infectious agent occurred following the 2009 H1N1 influenza pandemic. In China, the incidence of narcolepsy increased 3-fold in the six months after the peak of the

outbreak, then decreased to the normal rate of onset by 2011 after the pandemic had subsided [35]. As initially reported in Finland and Sweden [36] and subsequently in other European countries, a 6- to 9-fold increase in new narcolepsy cases in children was observed a few months following vaccination against H1N1 with Pandemrix, a formulation that contained the AS03 adjuvant. In contrast, no elevations in the rate of narcolepsy were reported in the US where only non-adjuvanted vaccines were used [37], or elsewhere in Europe, where the closely-related MF59 adjuvant was used in the H1N1 vaccine Focetria® (Novartis Vaccines & Diagnostics, 2007) [38]. Although these results suggest that the adjuvant AS03 could be problematic, no elevation in narcolepsy rates were observed in Canada where AS03 was also used as a component of the H1N1 vaccine Arepanrix® (GlaxoSmithKline, 2009) [39]. Although Pandemrix and Arepanrix were produced by the same manufacturer and administered with AS03, slightly different protocols for antigen isolation were utilized. This has led to a hypothesis that differential composition of the vaccines may have contributed to the increased incidence in narcolepsy in the affected populations [40].

Immunologic therapies

Assuming that narcolepsy is an autoimmune disease that targets Hcrt/orexin neurons, the most fundamental treatment would be prevention of its development using immunotherapies or neuroprotective strategies. This approach is challenging given that testing of treatments in well-controlled studies would require finding suitable numbers of cases of narcolepsy close to disease onset. In a case of childhood narcolepsy, the immunosuppressant prednisone failed to improve EDS and to prevent the development of cataplexy when administered 3 months after abrupt onset [20]. Furthermore, attempts to remove hypothesized autoantibodies with intravenous immunoglobulin (IVIg) have produced mixed results. Early attempts at IVIg therapy resulted in subjective improvement in EDS and cataplexy despite persistently low Hcrt1/orexin-A levels, but effects were not in seen in cases in which narcolepsy onset was a year or longer prior to IVIg [41]. However, IVIg administered very close to disease onset (15 days) normalized Hcrt1/orexin-A levels and resulted in clinical improvement in cataplexy [41]. More recent attempts using IVIg found that Hcrt1/orexin-A levels remained abnormal and any

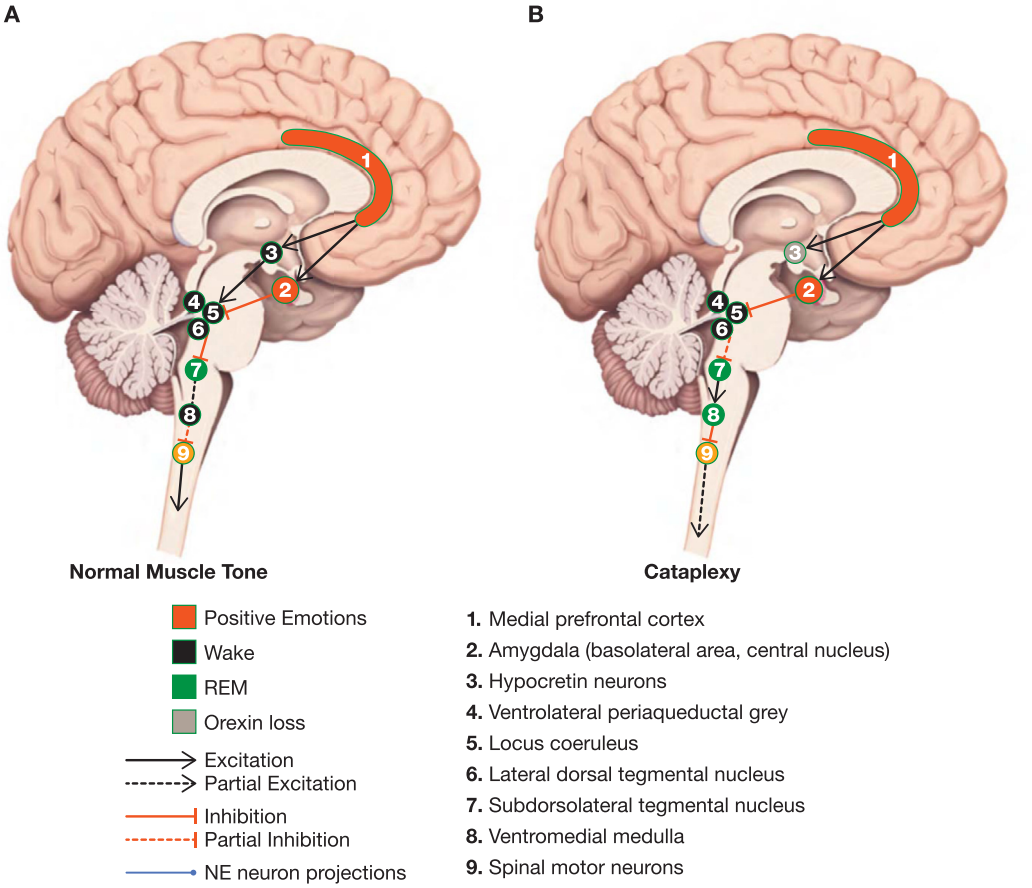
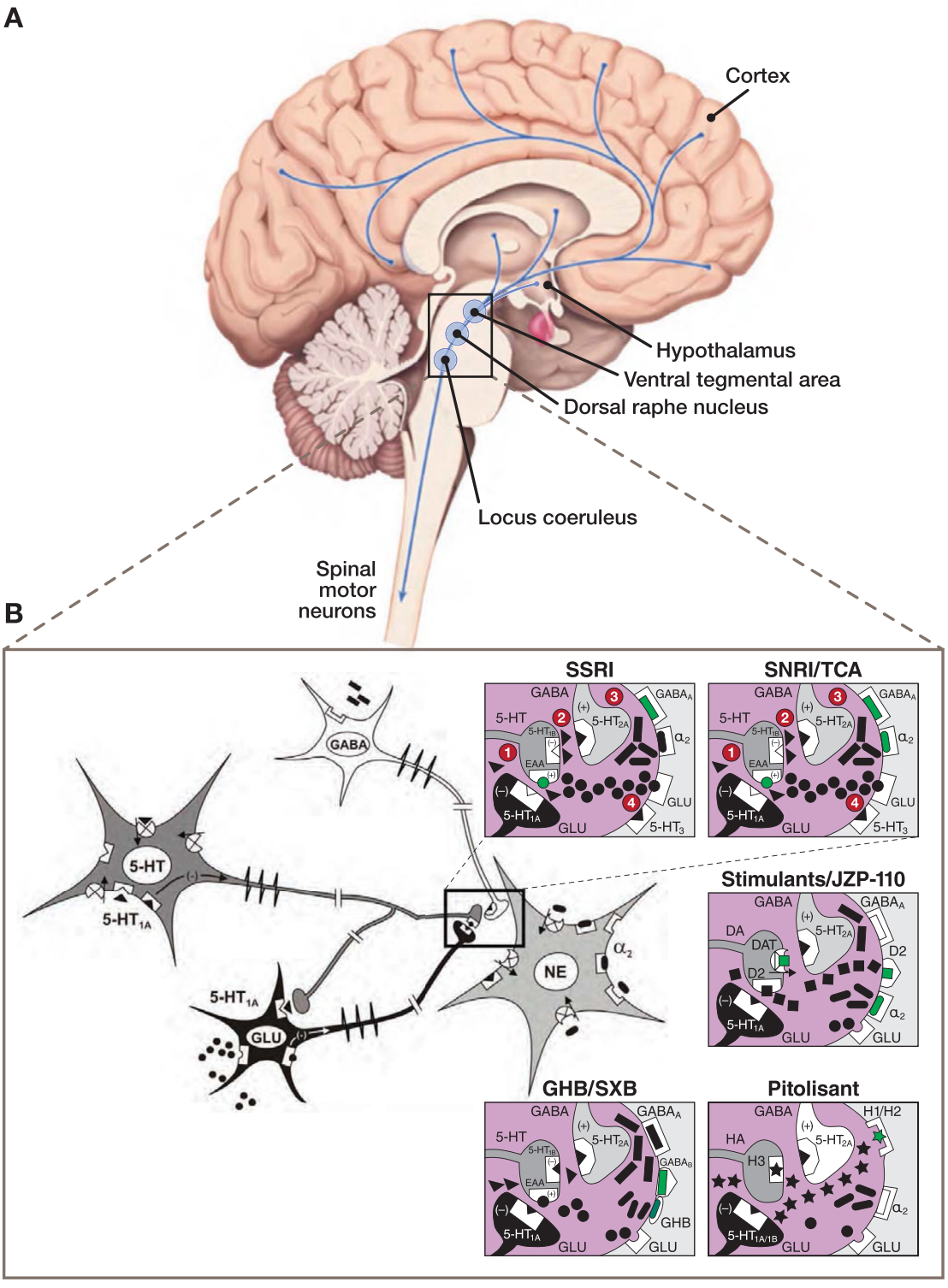


Fig. 1. Circuit mechanisms controlling cataplexy and Rapid Eye Movement (REM) sleep atonia. (Sagittal section of the human brain adapted from [103]). The subdorsolateral tegmental nucleus (SLD; 7) and ventromedial medulla (VM; 8) constitute the core circuits that generate rapid eye movement (REM) sleep atonia. When (presumably glutamatergic) SLD neurons become active, they stimulate gamma-aminobutyric acid (GABA)/glycine neurons in the VM such that they trigger REM sleep atonia by hyperpolarizing spinal motor neurons (MN; 9). **A)** In non-narcoleptics, positive emotions do not trigger muscle atonia because descending inhibition from GABAergic neurons in the central nucleus of the amygdala (CeA; 2) to the locus coeruleus (LC), laterodorsal tegmentum/pedunculopontine nuclei (LDT/PPT), and ventrolateral periaqueductal gray (vlPAG) is offset by excitatory hypocretin/orexin inputs (3), which prevent positive emotions from accessing the REM sleep circuits (i.e., SLD => VM) that trigger muscle atonia. **B)** In narcolepsy, there is decreased excitatory Hct input (3) to LC/LDT/PPT and vlPAG. Positive emotions activate cortical areas such as the medial prefrontal cortex (mPFC; 1) which innervate neurons of the basolateral area (BLA; 2) of the amygdala that project to GABA neurons in the CeA. GABAergic CeA neurons then inhibit the LC, LDT/PPT, and vlPAG, which in turn disinhibit the SLD, thereby allowing it to activate the VM to produce MN inhibition and hence muscle atonia/weakness during cataplexy. **Abbreviations:** BLA, Basolateral area; CeA, Central nucleus of the amygdala; GABA, Gamma-aminobutyric acid; LC, Locus coeruleus; LDT/PPT, Laterodorsal tegmentum/pedunculopontine nuclei; MN, Motor neurons; mPFC, Medial prefrontal cortex; NE, Norepinephrine; REM, Rapid eye movement; SLD, Subdorsolateral tegmental nucleus; vlPAG, Ventrolateral periaqueductal gray; VM: Ventromedial medulla.


A
Cortex
Hypothalamus
Ventral tegmental area
Dorsal raphe nucleus
Locus coeruleus
Spinal motor neurons
B
SSRI
SNRI/TCA
Stimulants/JZP-110
GHB/SXB
Pitolisant
GABA
5-HT
5-HT1A
GLU
NE
DA
DAT
D2
HA
H3
H1/H2
EAA
GHB
Key:
5-HT
GABA
NE
GLU
DA
HA
Transporter
Receptor Activation

symptom improvements tended to be temporary [42]. A greater understanding of the neuroimmunological factors that compromise the Hcrt/orexin system is needed to develop treatments aimed at prevention.

Neural circuit mechanisms in narcolepsy-cataplexy

Although the etiology of narcolepsy likely involves genetic suceptibility to immunological responses, the neural circuits underlying narcolepsy without cataplexy (NT2) have remained elusive, likely due to disease heterogeneity, spectrum of illness, and imprecise diagnoses. More is known about the neurobiology of narcolepsy with cataplexy (NT1) and the mechanisms responsible for muscle paralysis/weakness during cataplexy.

The loss of muscle tone during cataplexy is hypothesized to be caused by inappropriate recruitment of circuits that generate muscle atonia during REM sleep [43]. Multiple lines of evidence suggest that cataplexy and REM sleep paralysis share a common circuit mechanism. Imaging studies in narcoleptic patients indicate brainstem regions that are active during REM sleep are also active during cataplexy [44,45], and cell-recording studies in narcoleptic dogs show that the circuitry controlling REM sleep paralysis is similarly active during both cataplexy and REM sleep. For example, cells in the locus coeruleus (LC), whose inactivity suppresses skeletal muscle tone, cease their discharge during both cataplexy and REM sleep [46], and cells in the ventromedial medulla, a region that promotes REM sleep atonia, increase their firing rate during both cataplexy and REM sleep [47].

Recent experimental studies further support the concept that muscle atonia in cataplexy is triggered by the brainstem circuits that underlie muscle atonia in REM sleep. Chemogenetic activation of cells in the subdorsolateral tegmental nucleus (SLD), which generate REM sleep atonia, were found to induce cataplexy-like attacks in wild-type mice, whereas inactivation of these same cells markedly reduced cataplexy in narcoleptic mice. These findings provide behavioral evidence that the circuits that control REM sleep atonia also play a functional role in regulating muscle paralysis in cataplexy (Fig. 1A and B).

The link between emotional events and cataplexy onset suggests that the neural circuits that mediate emotional context are altered in narcolepsy. In narcoleptic dogs, cataplexy is triggered by food, play, or sex and, in narcoleptic mice, cataplexy is increased by arousing stimuli such as social reunion, access to running wheels, and the introduction of novel foods such as chocolate. The amygdala is a limbic structure involved in processing both positive and negative emotions that is also associated with REM sleep regulation and could therefore be part of a neural circuit in cataplexy. The link between the amygdala and cataplexy is supported by imaging studies showing that it is active during cataplexy [44], and cellular recordings in narcoleptic dogs indicate that neurons in the central nucleus of the amygdala (CeA) become active during cataplexy and become silent when cataplexy ends [48]. In narcoleptic orexin knockout mice, both chemically-induced lesions of the CeA and inactivation of gamma-aminobutyric acid (GABA) cells in the CeA reduce cataplexy, whereas activation of GABAergic CeA cells exacerbates cataplexy likely through postsynaptic $GABA_A$ and $GABA_B$ receptor-mediated circuit dysfunction [49–51]. Genetic-driven expression of the Hcrt/orexin peptides within the amygdala also suppresses cataplexy in narcoleptic mice [52], further suggesting that the amygdala is involved in controlling cataplexy.

Cells in the CeA may function as a “relay center” between the cortical structures that interpret emotional stimuli and the brainstem circuits that generate motor paralysis during cataplexy (Fig. 1A and B). This hypothesis stems from research demonstrating that rewarding conditions activate the medial prefrontal cortex (mPFC) which innervates circuits within the amygdala [53]. Connections between the mPFC and CeA are integral in promoting cataplexy because removing either of them suppresses cataplexy in orexin knockout mice [54]. GABAergic projection neurons are the primary output pathway from the CeA [53] and these cells innervate the LC, lateral pontine tegmentum (LPT), and ventrolateral periaqueductal gray (vlPAG), which collectively function to facilitate waking muscle tone by silencing atonia-generating regions in the SLD. Indeed, lesions of the LPT/vlPAG [55] and reduced NE release from the LC [54] can trigger cataplexy-like attacks in awake rodents. Positive emotions may therefore elicit cataplexy by activating the mPFC which excites GABAergic CeA projection neurons that, in turn, inhibit the LC, LPT, and vlPAG, thereby generating muscle paralysis by disinhibiting the SLD (Fig. 1A and B). In healthy people, strong positive emotions do not initiate muscle paralysis because Hcrt/orexin cells excite the LC, LPT, and vlPAG, which prevents disinhibition of SLD cells. However, in narcolepsy, Hcrt/orexin cell loss upsets this balance, so that GABAergic CeA cells are unopposed in inhibiting the LC, LPT, and vlPAG,

Fig. 2. A) NE neuron projections (blue) widely innervate the human brain (adapted from [103]). LC NE neurons send ascending projections to the cortex that facilitate wakefulness and descending projections to the spinal cord that are important in maintaining muscle tone. LC NE neurons receive a prominent excitatory projection from Hcrt/orexin neurons in the tuberal hypothalamus. The loss of excitatory drive onto LC NE neurons due to Hcrt/orexin neuron compromise in narcolepsy can lead to EDS (i.e., lack of NE tone to the forebrain). Dysregulated LC NE neurons may also permit reduced muscle tone in response to GABAergic input from the amygdala, resulting in cataplexy in response to emotional stimuli. **B)** A schematic brainstem circuit (adapted from [59]) depicting 5-HT neurons from the dorsal raphe, as well as glutamate and GABA projections to the LC, which are modulators of NE activity. 5-HT exerts a tonic inhibitory tone on LC NE neuron activity and LC NE neurons provide an excitatory tone to 5-HT neurons (not illustrated). Glutamate and GABA in the LC impacts NE neuron firing directly and by modulating 5-HT input. Medications used in the treatment of narcolepsy increase NE release and/or availability with changes onto LC NE neuron activity. **a) SSRIs**: Desensitization of 5-HT autoreceptors ($5\text{-}HT_{1A}$ and $5\text{-}HT_{1D}$) during prolonged SSRI treatment leads to increased 5-HT transmission. 1) Desensitization of $5\text{-}HT_{1A}$ heteroceptors on glutamate neuron projections to the LC and increased activation of excitatory amino acid (EAA) receptors on 5-HT terminals (green circle) contributes to 2) increased 5-HT activation of $5\text{-}HT_{2A}$ receptors on GABAergic projections (green bar). 3) SSRIs reduce NE neuron stimulation and activity by increasing $GABA_A$ receptor activation in the LC (green bar) and 4) increased $5\text{-}HT_3$ receptor activation (likely on NE terminals) can enhance NE in postsynaptic structures. **b) SNRIs/TCAs**: In addition to effects as outlined in (**a**), SNRIs and TCAs also produce an increase in NE availability due to NE reuptake transporter blockade. This results in increased activation of α_2-autoreceptors (green pill on NE neurons) and reduced activity and stimulation of LC activity. **c) Amphetamines/Sympathomimetics/JZP-110 (solriamfetol)**: Alerting medications increase the release and/or reuptake of NE and DA (depending on the medication) and produce similar effects on LC NE neuron activity as SNRIs and TCAs. **d) GHB/SXB:** Activation of $GABA_B$ receptors on NE neurons reduces LC activity and discontinuation produces an increase in LC NE neuron activity. Given the short half-life (30 min–1 h) of SXB, the nighttime sedative effects wane, and increased LC NE neuron stimulation and activity ensues during the day; hence, its effectiveness in treating both EDS and cataplexy in narcolepsy. **e) Pitolisant:** Modulation of H_3 autoreceptors (inverse agonist/antagonist) on histamine neurons in the tuberomammillary nucleus produce increased histamine release onto LC NE neurons. LC NE neurons increase in activity following binding to H_1 and H_2 receptors on NE neurons, which is effective in treating both EDS and cataplexy in narcolepsy. **Abbreviations:** α_2, Type 2 alpha adrenergic receptor; DA, Dopamine; D_2, Type 2 DA receptor; DAT, DA transporter; EAA, Excitatory amino acid; EDS, Excessive daytime sleepiness; GABA, Gamma-aminobutyric acid; $GABA_A$, Type A GABA receptor; GHB, Gamma-hydroxybutyrate; GLU, Glutamate; HA, Histamine; H_1, Type 1 HA receptor; H_2, Type 2 HA receptor; H_3, Type 3 HA receptor; Hcrt, Hypocretin; 5-HT, Serotonin; $5\text{-}HT_{1A}$, Type 1A 5-HT receptor; LC, Locus coeruleus; NE, Norepinephrine; SNRI, Serotonin norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitor; SXB, Sodium oxybate; TCA, Tricyclic antidepressant.

thereby creating a circuit environment conducive to muscle atonia and cataplexy.

LC NE neuron activity and narcolepsy-cataplexy

Given the aberrant neural circuitry in narcolepsy described above, pharmacologic manipulations that regulate the LC proper or its afferents represent effective classes of therapeutics in narcolepsy and sleep-wake disorders. The LC proper is a largely homogeneous structure of densely-packed NE neurons that also express multiple neuropeptides. Neuronal dendrites from the LC core extend into the pericoerulear region which contains a dense collection of GABA neurons, including the SLD. Whereas the LC proper has been reported to primarily receive inputs from the ventrolateral and dorsomedial rostral medulla (paragigantocellularis and prepositus hypoglossi nuclei, respectively) as well as hypothalamus, the pericoerulear region is targeted by inputs from a variety of sources including prefrontal cortex, amygdala, lateral hypothalamus and dorsal raphe. LC neurons are responsible for approximately 90% of the NE in the forebrain and are believed to be important in mediating wakefulness and arousal states. It is well appreciated that LC NE neurons begin to discharge upon awakening from sleep and are extremely active in emotional situations such as arousal, fear, and threat [56]. Conversely, during times of sleepiness, the discharge rate of LC NE neurons begins to decline and LC NE neurons become quiescent in REM sleep [56]. LC activity is linked to clinical disorders of fear, arousal, and sleep, such as in posttraumatic stress disorder, anxiety, and insomnia [57,58].

LC neurons, when dysregulated, likely contribute to pathologic changes in sleep and associated disorders such as narcolepsy-cataplexy. It is increasingly clear that therapeutics may provide symptomatic relief in patients with narcolepsy and cataplexy through regulation of LC NE neuron activity. Brainstem neurons exert local modulation onto LC NE neuron activity through complex neural circuits (see Figs. 1 and Figs. 2). Ascending LC NE neuron projections to the forebrain mediate cortical arousal, whereas descending projections to the spinal column affect muscle tone. It has been suggested that the activity of LC NE neurons can be halted during limbic activation and can lead to cataplexy [46].

The therapeutic benefit of antidepressants in narcolepsy and cataplexy may result from modifications in serotonin (5-HT) and NE neuron neurotransmission, which results in increased regulation of LC activity. This concept can be illustrated by considering sleep-wake medications that are derived from the 5-HT synthetic pathways or changes in catecholamine neurotransmission, such as melatonin agents (i.e., ramelteon, agomelatine) and some alerting medications (i.e., methylphenidate), respectively. 5-HT is a precursor to melatonin production and ingestion of melatonin is linked to sleep and regulation of circadian rhythms, whereas alerting medications enhance catecholamine availability (i.e., NE and DA) and promote arousal. Interestingly, agomelatine (an antidepressant with melatonin and 5-HT receptor affinity) binds to 5-HT_2 receptors and augments LC NE neuron activity by decreasing GABAergic tone, which likely relates to its arousal-promoting properties [59,60]. Modulation of regulatory inputs onto the LC, such as with agents that affect 5-HT and NE neuron activity, appear to be critical to maintain sleep-wake states, but more clinical research is needed to determine whether agents with melatonin and 5-HT properties can contribute to management of narcolepsy-cataplexy.

5-HT neurons and LC NE regulation of sleep-wake states

Brainstem 5-HT neurons are prominent regulators of sleep-wake cycles [61], likely through their widespread projections throughout the neuraxis. One prominent connection implicated in maintaining sleep and wakefulness is predicated on reciprocal interactions between 5-HT neurons in the dorsal raphe (DR) and LC NE neurons. These nuclei are located in the brainstem in close proximity and are components of the reticular formation (Fig. 2A). The reticular formation is associated with both changes in sleep-wake states and consciousness through reticular activating system and muscle tone by way of spinal afferents through the reticulospinal tract. Reciprocal excitatory-inhibitory circuits in the brainstem are prominent regulators of 5-HT and NE neuron activity (Fig. 2B). 5-HT regulation of the LC occurs, in part, through a tonic inhibitory tone from the DR which involves a complex circuit of glutamate-GABA neuron interactions to maintain NE neuron firing integrity [59,60]. In turn, DR 5-HT neurons are activated by LC NE neurons through α_1-heteroceptors. Glutamate and GABA neurons, which regulate LC NE neuron activity, originate in the periaqueductal gray and medulla; these cell groups have also been implicated as regulators of sleep [62]. Hcrt neurons activate the vlPAG which provides GABAergic inputs to DR 5-HT and LC NE neurons that are involved in REM sleep [63]. Compromise in the modulation between 5-HT and NE neurons and their afferents would have direct neurobiological ramifications in sleep-wake disorders with affective components, particularly that of narcolepsy with cataplexy. These reciprocal interactions between 5-HT and NE neurons have been probed in numerous fundamental studies using pharmacologic manipulations, many of which have had an impact in symptom management in patients with narcolepsy and cataplexy [64]. Agents that target 5-HT and NE neurons and impact the regulation of LC activity and thereby ameliorate the symptomatology of narcolepsy and cataplexy will be discussed below.

Effects of antidepressants on LC NE neuron activity and relevance in narcolepsy-cataplexy

Antidepressants used in the treatment of narcolepsy-cataplexy predominantly target 5-HT and NE neurons, monoamines with known effect on sleep-wakefulness and sleep architecture. Modifications in monoamine neuron regulation with antidepressants over a sustained treatment period can provide benefit in some individuals with narcolepsy and cataplexy [65]. Selective 5-HT and NE reuptake inhibitors (SNRIs) are not only regarded as the gold-standard antidepressant class used in the treatment of mood and anxiety disorders, but also provide benefit in patients with narcolepsy and cataplexy. Antidepressants are agents that increase the availability or neurotransmission of 5-HT and NE, in part, through modifications of both presynaptic and postsynaptic monoamine receptors. For instance, changes in 5-HT_{1A} and 5-HT_{1D} autoreceptors in response to chronic antidepressant treatments modulate 5-HT neuron firing activity and neurotransmitter release. In the presence of 5-HT transporter reuptake blockade, such autoreceptor modifications increase monoamine availability with sustained administration. The delayed onset of action of these medications parallels their neurobiological effects on regulation of both 5-HT and NE neuron activity, thereby providing pharmacologic credence to monoamine neuronal interactions as viable therapeutic targets [64]. This therapeutic approach is perhaps best exemplified in the clinic with use of the

antidepressant venlafaxine, an SNRI that has shown benefit in treatment of narcolepsy/cataplexy–associated depression [66]. By targeting both 5-HT and NE reuptake processes, regulation in the firing activity of these monoamines occurs due to their monoamine-receptor adaptations. Fig. 2B presents a schematic illustrating the interactions between 5-HT and NE neurons and that of antidepressant effects.

Hcrt neurons, SXB, and LC NE regulation

Hcrt/orexin–producing neurons in the tuberal hypothalamus are compromised in subtypes of patients with narcolepsy; these cells innervate the LC and exert a tonic excitatory tone on NE neurons. Hcrt neuron degeneration leads to LC dysregulation and compromised NE neuron firing activity that can permit episodes of cataplexy during the day in narcoleptic patients and during the dark (active) period in narcoleptic rodents. One treatment pathway by which cataplexy episodes may be overcome in Hcrt/orexin-deficient individuals would be to enhance the activity and regulation of LC NE neurons using medications. For instance, gamma-hydroxybutyrate (GHB) is a metabolite of GABA that is produced in the brain through the semialdehyde reduction pathway with affinity for GABA receptors (predominantly $GABA_B$), and both $GABA_A$ and $GABA_B$ receptors have been localized in the LC [67]. $GABA_B$ receptors are G protein–coupled and exert inhibitory effects on LC NE neuron firing activity and responsiveness [68]. SXB (a sodium salt of GHB) is a treatment for narcolepsy that reduces daytime sleepiness and cataplexy when dosed at night [69]. SXB leads to cessation of LC NE neuron firing activity and promotion of nocturnal sleep in individuals with narcolepsy [68]. The half-life of SXB is between 30 and 60 min and requires the patient to receive dosing twice during the night. This repeated dosing may result in nighttime suppression of LC NE neurons and a "rebound effect" of LC NE neurons with increased responsiveness to stimuli during the daytime to sustain wakefulness [68]. The effect of SXB on nocturnal sleep consolidation likely also contributes to less sleepiness during the day. Thus, improved alertness and mitigation of cataplexy symptoms during the daytime in patients treated with SXB at night may reflect the modulatory effects of SXB on LC NE neuron activity [68] (Fig. 2B).

Midbrain DA neurons as treatment targets in narcolepsy-cataplexy

DA neurons in the ventral tegmental area (VTA) [70] and the DR [71] also contribute to the regulation of sleep/wake. VTA DA neurons are the origin of the mesolimbic system and project to forebrain structures, particularly to the nucleus accumbens, a brain region regarded as part of the neural reward circuitry and cataplexy. Hypothalamic (A11) DA neurons regulate cataplexy in narcoleptic dogs [72] and, in mice deleted of the orexin gene, sleep attacks and cataplexy was modulated by D_1- and D_2-receptors, respectively [73]. Similar to A11 DA neurons, VTA DA neurons also send descending projections to the brainstem and can increase the activity of DR 5-HT neurons and decrease the firing rate of LC NE neurons. DR 5-HT neurons, unlike LC NE neurons, do not have D_2 receptors, but both are inhibited by VTA DA neuron activation and D_2 receptor agonists. Although DA binds to D_2 receptors in the LC, the inhibitory effects of DA likely result from activation of α_2-autoreceptors which are linked to REM sleep. Given that DA is a precursor for NE synthesis, it is noteworthy that LC neurons have recently been documented to release DA as well as NE [74], which supports the concept that the inhibitory effects of DA on NE neuron activity is mediated through autoinhibitory α_2-adrenoceptors.

The stimulatory effects of DA and NE from the LC on 5-HT neuron activity is mediated through activation of D_2 and α_1-receptors, respectively. Catecholamine releasers and/or reuptake inhibitors increase DA and NE in the forebrain and thereby enhance attention and wakefulness. These agents also increase catecholamines, increase 5-HT neuron activity, and decrease LC NE neuron activity. Modifications in monoamine receptor activation to medications that target catecholamine neurons is relevant to reduction of EDS and cataplexy in patients with narcolepsy.

Bridging neurobiology with current treatments in narcolepsy-cataplexy

Although prevention of narcolepsy would be optimal, the current goals of treatment are restoration of nocturnal sleep, decrease in cataplexy frequency, reduction of abnormal dream phenomena, improvement of alertness and sleepiness, improvement of quality of life and improved safety. However, current therapeutic interventions remain far from ideal; more effective and specific treatments are clearly needed. Only a few pharmacological treatments have gained specific regulatory approval for the treatment of narcolepsy and the majority of them work only for one symptom. Most of the treatments act on several neurotransmitters, their effects are dose-dependent, and their pharmacological effect on the neural networks involved in the generation of narcolepsy symptoms are not well understood. EDS as measured by Epworth Sleepiness Scale (ESS) shows improvement for all stimulants, but rarely normalization to an ESS score <10 is achieved. Cataplexy has only been assessed in studies after 2000, mainly by diaries, and effects on sleep paralysis, hypnagogic hallucinations, and nocturnal sleep have rarely been reported. Treatments directed at neurobiological circuits that can be translated clinically and tethered to specific symptom management may lead to personalized approaches. This approach is consistent with the Research Domain Criteria initiative spearheaded by the National Institutes of Mental Health (https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml).

An overview of medications used in the treatment of narcolepsy-cataplexy is provided below.

Amphetamines

Amphetamines have been used to treat narcolepsy since the 1930s. The effect of amphetamine on DA release is dose-dependent; at lower doses, amphetamines release NE whereas, at higher doses, reuptake transporters are also inhibited. It is noteworthy that the NE reuptake transporter is also important for clearing DA from the synapse [75]. The increased availability of these catecholamines has been linked to their wake-promoting effects. Adderall (immediate release) is a mixed amphetamine salt that is FDA-approved (not approved in Europe) for the treatment of narcolepsy. D-amphetamine (e.g., Dexedrine), lisdexamphetamine (Vyvanse), and other amphetamine medications exert similar effects to those of Adderall and are used off-label. D-amphetamine is effective in treating EDS in doses ranging from 10 to 60 mg. The elimination half-life of the amphetamines ranges from 10 to 30 h. Adverse effects include irritability, hyperactivity, mood changes, headache, palpitations, sweating, tremors, anorexia and insomnia, and are liable for abuse and addiction. Tolerance frequently occurs with these medications and represents a barrier to continued efficacy in the treatment of narcolepsy.

Methylphenidate

Similar to amphetamines, methylphenidate increases DA and NE release but has minimal effects on catecholamine storage. Methylphenidate is easily absorbed and readily passes through the blood–brain barrier, which results in rapid wake-promoting effects. The half-life of the non–slow release form is 2.7 h. A dose of 10–60 mg/day has been shown to significantly improve EDS. Notably, methylphenidate has fewer adverse effects on appetite and the cardiovascular system than amphetamines, but is liable for abuse. Patients with low CSF Hcrt1/orexin-A levels have a low risk for dependency [2].

Mazindol, a weight reduction medication with similarities to amphetamine, targets NE, DA and 5HT reuptake inhibition and is used off-label in the treatment of narcolepsy in Europe.

Modafinil and armodafinil

Modafinil is an approved stimulant for the treatment of narcolepsy in the USA and Europe. Positron emission tomography data indicate that modafinil blocks the DA transporter, resulting in an increase of DA in the CNS [76]. LC NE neuron firing and transition of these neurons into high phasic activity results from administration of modafinil in research subjects [77]. Modafinil blocks the reuptake of noradrenaline by the noradrenergic terminals on sleep-promoting neurons in the ventrolateral preoptic area, which may be partially responsible for its wake-promoting effect [78]. Modafinil reaches maximal plasma levels within 2 h. Metabolized in the liver into two inactive forms, its elimination half-life is 9–14 h and steady state is reached after 2–4 days. Modafinil can affect medications metabolized by cytochrome P450 enzymes, potentially increasing the serum concentrations of TCAs, SSRIs, warfarin, and reducing the efficacy of oral contraceptives. Doses of modafinil at 200–400 mg once or twice a day reduce EDS significantly, as measured by maintenance of wakefulness test (MWT) and ESS [79]. When compared with the above-mentioned alerting medications, the risk for dependency, development of tolerance, and impulsive behavior is low. A few cases of mania have been reported in patients with known or unknown psychiatric disorders. Moreover, some domains of quality of life have been shown to be significantly improved by modafinil. Common adverse effects are irritability, palpitation, sweating, headache, tremor, nausea, and (rarely) skin rash.

Armodafinil (approved in the USA, not approved in Europe) is the R-enantiomer of modafinil and is also used in the treatment of narcolepsy. The half-life and the adverse effect profile for armodafinil is about the same as for modafinil. However, the plasma concentration is higher and longer lasting and may result in a more prolonged effect of the drug. In a randomized controlled study using the MWT as the primary outcome measure, armodafinil significantly increased sleep latency at doses of 150–250 mg given once per day [80].

Solriamfetol (JZP-110)

Solriamfetol is a selective DA and NE reuptake inhibitor that is awaiting FDA approval for the treatment for EDS in narcolepsy. Ninety percent of the drug is eliminated unchanged via the kidneys. Solriamfetol has a maximum concentration (t_{max}) after 1.3–2.5 h, a half-life of 6–7.6 h, with a steady plasma level after about three days. In patients with narcolepsy, three randomized controlled studies of solriamfetol 150 and 300 mg showed a significant, immediate, and stable dose-dependent improvement in sleep latency on the MWT, ESS score, and patient global impression of change [81]. Headache, nausea, decreased appetite, nasopharyngitis, dry mouth, and anxiety were the most commonly reported adverse effects in a Phase 3 clinical trial [82]. No REM or non-REM rebound was reported after withdrawal in studies with healthy volunteers.

GHB and SXB

GHB was initially found to be clinically useful for treating narcolepsy in the early 1970s, which prompted worldwide studies and subsequent regulatory approval for SXB, a sodium salt of GHB. SXB was approved as an anticataplexy medication in the US in 2002, in Europe in 2005 and as a treatment for EDS in 2005. Several international studies have shown a significant, dose-dependent reduction of cataplexy with SXB (4.5 g: 57%, 6 g: 65%, 9 g: 84.7%) [83]. A study performed over 7–44 months also showed a gradual reduction of the anticataplexy effect but no precipitous recurrence of cataplexy events.

GHB occurs endogenously in micromolar concentrations in body tissue and the brain. It passes the blood–brain barrier quickly and binds with differential affinity to predominantly $GABA_B$ receptors and induces slow-wave activity in the EEG [84]. The elimination half-life is short at 30 min–1 hour; therefore, SXB needs to be dosed twice per night (2×2.25–4.5 g) as it is metabolized via the Krebs cycle. It is the only substance with a proven long-term effect on nocturnal sleep; it also improves EDS and reduces sleep paralysis and hypnagogic hallucinations.

In a post-authorization, non-interventional surveillance study [85], 740 patients treated with sodium oxybate were monitored for $\leq$18 months. Of these, 67.3% experienced treatment-emergent adverse events, most frequently headache (11.6%) and nasopharyngitis (6.4%). Discontinuation due to treatment-emergent adverse events (TEAEs) was 8.8% and the incidence of serious TEAEs was 6.4%. No case of addiction was reported. Regarding time to response, the median (95% CI) times to first response were 37 (31–50) days for EDS and 25 (17–29) days for cataplexy, and median times to maximum response were 106 (85–164) days for EDS and 213 (94–279) days for cataplexy [83]. Although it is not primarily an alerting medication, SXB improves EDS dose-dependently when administered during the nighttime. As described above, SXB has been hypothesized to improve daytime wakefulness by augmenting LC NE neuron and/or enhancing DA activity during the day [68]. ESS and MSLT scores show significant improvements with 2×3–4.5 g/night [86]. SXB has an additive effect when administered in combination with modafinil [86].

Pitolisant

Histaminergic neurons, along with other neurotransmitters, contribute to sustained wakefulness. Pitolisant is an inverse histamine H_3-autoreceptor agonist that releases histamine in nanomolar concentrations in the brain to activate LC NE neurons [87]. In the rat, pitolisant increases ACh and DA in the prefrontal cortex and ACh in the hippocampus [88]. In Hcrt knockout mice, pitolisant causes prolonged wake episodes and reduces narcolepsy-like symptoms [89]. Elimination is hepatic and metabolites are excreted via the kidneys and exhalation. Pitolisant has a half-life of 10–12 h and therefore needs to be administered only once daily [89]. T_{max} plasma levels are reached after 1–3 h and a steady state is established after about 6 days. Pitolisant was approved by the European Medicines Agency in 2016; recommended doses are 4.5–36 mg. Pitolisant is available for adults in the USA in an open-label, early access program (EAP) while

awaiting FDA approval; recommended doses in the US are 8.9–36 mg.

Pitolisant improves EDS as measured by the ESS and MSLT. A comparative study with modafinil showed that pitolisant had similar effects on EDS [90]. The adverse effects of pitolisant are insomnia, headache, abdominal discomfort, dizziness, anxiety, diarrhea, and nausea. In animals, no genetic or carcinogenic effects could be found; however, pitolisant may reduce food intake in young animals and produce hypoactivity, tremor, clonic attacks, and gait problems at very high doses. A recent long-term study with more than 50 patients demonstrated a significant improvement on cataplexy. The reduction of cataplexy on monotherapy was as large as the reduction experienced by patients that were additionally treated with anticataplectic and alerting medication therapy [91]. Pitolisant also has antagonist activity at sigma-2 receptors and is an agonist of sigma-1 receptors, causing a possible risk for depression and addiction [90].

TCAs

In the 1960s, imipramine, desmethylimipramine, clomipramine, and protriptyline were used to treat cataplexy. These compounds suppress REM sleep and facultative symptoms such as sleep paralysis and hypnagogic hallucinations. Clomipramine (approved by FDA and EMA for treatment of cataplexy) is still widely used and works as a 5-HT transporter reuptake inhibitor that quickly metabolizes into desmethylclomipramine, inhibiting adrenergic reuptake. Clomipramine at a dose of 25–75 mg produced a reduction of both cataplexy severity and frequency [92], but is also effective at lower doses of 10–20 mg. Adverse effects are mainly caused through anticholinergic effects (i.e., dry mouth, sweating, constipation, tachycardia, weight gain, hypertension, and difficulty voiding). Other clinically meaningful effects include sexual dysfunction, weight gain, drug interactions. Clinically relevant serious adverse event risks may include cardiovascular effects and seizure, however, no long-term studies are available. Withdrawal may cause “rebound cataplexy” and tolerance may occur. Due to the absence of studies showing strong evidence of efficacy and unfavorable side effect profile, TCAs are no longer considered first - line treatment for cataplexy, sleep paralysis and hypnagogic hallucinations.

SSRIs

Compared with TCAs, SSRIs selectively inhibit 5-HT reuptake transporters and therefore higher doses are required. None of the SSRIs have been studied using a randomized placebo-controlled trial design for reducing cataplexy symptoms in narcolepsy patients. However, a dose range of fluoxetine at 20–60 mg is reported to cause a mild reduction of cataplexy. Citalopram [93] and escitalopram [94] have been reported to reduce cataplexy significantly in small samples of patients. Withdrawal of SSRIs can cause cataplexy symptoms to precipitously occur in narcoleptic patients. Common adverse effects are irritation, gastrointestinal and sexual problems, and movement disorders.

SNRIs

Enhancement of NE and 5-HT activity may reduce cataplexy by inhibiting “REM-on” neurons in the lateral dorsal tegmentum and pedunculopontine tegmentum. Venlafaxine (used off - label in the USA and Europe) 150–375 mg/day was tested in four patients with narcolepsy over 2–7 months [95]; EDS and cataplexy improved in all patients. Of the SNRIs, venlafaxine is widely used due to its potent effect on cataplexy, similar to that of clomipramine. A recent study in six children showed reduction of cataplexy and, in two children, of nightmares and hypnagogic hallucinations as well [96]. Side effects are similar to SSRIs and include sweating, increased heart rate and blood pressure. Status cataplecticus on withdrawal has been reported [97]. Pilot studies with atomoxetine and duloxetine also showed improvement of cataplexy and EDS [98].

Future directions

To date, the development of medications to treat narcolepsy has largely involved the use of drugs that have been developed for other medical disorders, modafinil being one prominent exception. The discovery of the Hcrt neuron loss as the proximate cause of narcolepsy has enabled the creation of animal models with both construct and face validity [4], thereby enabling assessment of currently used medications to determine predictive or pharmacological validity of these models [99] as well as assessment of the utility of these models to help identify new therapeutic paths for treatment of both EDS and cataplexy [100]. Although prevention, or at least mitigation of, Hcrt neuron loss is the ultimate treatment for this disorder, absent a complete understanding of the underlying reason for this cell loss, replacement of the Hcrt peptide function is the most appropriate novel therapeutic pathway. In this regard, the description of the first small molecule Hcrt receptor agonist [101] and its apparent efficacy in an appropriate mouse model [102] are welcome developments.

Conclusion

Narcolepsy is a disabling disorder that is likely underdiagnosed. Currently available treatments are associated with symptomatic improvement. Given the spectrum of illness, different etiologies, and heterogeneity of disease presentation, therapeutic strategies in narcolepsy often require multimodal targets and polypharmacy. Recognition and characterization of central neuroanatomical regions such as the LC, DR, and amygdala, their neural pathways and associated neurotransmitters such as NE, 5-HT, histamine, and GABA (as well as the GABA metabolite GHB), have led to a better understanding of the disease state of narcolepsy. The mechanism of action of established therapies, such as alerting agents and anticataplectic medications, to treat EDS and cataplexy closely follows their neurotransmitter effects, particularly that of modulating monoamine systems. Research into compromised Hcrt/orexin–signaling appears to be a causative factor of dysregulated neural circuit activity and reduced excitatory drive onto LC NE neurons, which neurobiologically is linked to cataplexy and EDS. Most treatments effective in narcolepsy-cataplexy target or enhance catecholamine availability (amphetamines, methylphenidate, modafanil/armodafanil, TCAs, SNRIs, JPZ-110/solriamfetol) and can regulate daytime LC NE neuron activity (SXB, SSRIs and pitilosant). Advances in the understanding of the immunogenetic and environmental contributions to the etiology of narcolepsy could potentially lead to the development of preventive measures and effective immunotherapeutic interventions, particularly at disease onset.

Practice Points

Narcolepsy types 1 and 2 are associated with excessive daytime sleepiness (chronic daily sleepiness for $\geq$ 3 months) and represent a spectrum of illness with differences in response to treatments based on presumptative neuropathophysiology:

1. Response to alerting medications with distinct neurobiological targets (amphetamine, methylphenidate, modafinil/armodafinil, solriamfetol [JZP-110]), antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors), sodium oxybate, and the H_3-receptor inverse agonist/antagonist pitolisant have demonstrated efficacy as narcolepsy treatments in clinical trials, but exert varying effects in patients, and combination treatments continue to represent the mainstay practice for symptom management.
2. Enhanced catecholamine availability and regulation of locus coeruleus norepinephrine neuron activity is likely central to the therapeutic activity of most of these compounds in patients with narcolepsy, but also vary in patients due to underlying neurobiological differences. Surrogate markers of LC NE neuron activity with clinical applicability may help in monitoring narcolepsy symptoms and contribute to treatment practices.
3. Only a few of these pharmacological treatments have gained specific regulatory approval for the treatment of narcolepsy and most of them are indicated for only one symptom. Approximately 50% of patients remain undertreated and continue to have daily episodes of cataplexy, EDS, inattentiveness, and fatigue. Misdiagnosis of narcolepsy in children is common and approved medications for children with narcolepsy do not exist. Clinical practice rendering evaluation and treatment of narcolepsy continues to be mainly based on expert experience.

Research Agenda

Delineating the dysfunctional neural circuits in narcolepsy may facilitate understanding the mechanism of action of current medications and guide development of novel treatment strategies by focusing research efforts on:

1. Genetic suceptibility and autoimmune compromise of hypocretin1/orexin-A that permits subdorsolateral tegmental nucleus- and ventromedial medulla-mediated cataplexy.
2. How to prevent hypocretin/orexin cell loss and offset unopposed recruitment of GABAergic central nucleus of the amygdala neurons to strong positive emotions which mediate locus coeruleus, lateral pontine tegmentum, and ventrolateral periaqueductal gray inhibition.
3. Therapeutics which are able to enhance both catecholamine availability (i.e., amphetamines, methylphenidate, modafinil/armodafinil, TCAs, SNRIs, JZP-110/solriamfetol) and regulation of daytime LC activity (SXB, SSRIs and pitilosant) for improved symptom management.

Conflicts of interest

Dr. Szabo has an investigator-initiated grant from Otsuka Pharmaceuticals and funding support from the National Institutes of Health (NIH) and the Brain Behavior Research Foundation (formerly known as NARSAD). He has served on the advisory board for Jazz Pharmaceuticals and as a consultant/speaker for Neurocrine Biosciences, Teva Pharmaceutical Industries Ltd, and Otsuka/Lundbeck Pharmaceuticals.

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