Cataplexy—clinical aspects, pathophysiology and management strategy

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Abstract | Cataplexy is the pathognomonic symptom of narcolepsy, and is the sudden uncontrollable onset of skeletal muscle paralysis or weakness during wakefulness. Cataplexy is incapacitating because it leaves the individual awake but temporarily either fully or partially paralyzed. Occurring spontaneously, cataplexy is typically triggered by strong positive emotions such as laughter and is often underdiagnosed owing to a variable disease course in terms of age of onset, presenting symptoms, triggers, frequency and intensity of attacks. This disorder occurs almost exclusively in patients with depletion of hypothalamic orexin neurons. One pathogenetic mechanism that has been hypothesized for cataplexy is the activation, during wakefulness, of brainstem circuitry that normally induces muscle tone suppression in rapid eye movement sleep. Muscle weakness during cataplexy is caused by decreased excitation of noradrenergic neurons and increased inhibition of skeletal motor neurons by γ-aminobutyric acid-releasing or glycinergic neurons. The amygdala and medial prefrontal cortex contain neural pathways through which positive emotions probably trigger cataplectic attacks. Despite major advances in understanding disease mechanisms in cataplexy, therapeutic management is largely symptomatic, with antidepressants and γ-hydroxybutyrate being the most effective treatments. This Review describes the clinical and pathophysiological aspects of cataplexy, and outlines optimal therapeutic management strategies.

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Introduction

Cataplexy is defined as sudden involuntary muscle weakness or paralysis during wakefulness, typically triggered by strong emotions, and is the pathognomonic symptom of narcolepsy with cataplexy—a sleep disorder that affects 0.06% of the adult population.[1,2] In addition to cataplexy, narcolepsy is characterized by sleep paralysis, sleep-onset rapid eye movement (REM) periods, hypnagogic hallucinations, and fragmented night-time sleep.[3,4] Cataplexy is virtually exclusive to patients with narcolepsy, and is the optimal behavioural biomarker of this disease.[2–4] Excessive daytime sleepiness (EDS) is usually the presenting symptom of narcolepsy, and cataplexy often develops within 1 year of birth and persists for life, although some patients report a delay between EDS and the onset of cataplexy of more than 5 years.[5] The age of onset of narcolepsy ranges from early childhood (with 5% of patients in the prepubertal stage) to the fifth decade, with a bimodal distribution that peaks at 15 years and 35 years of age.[5] Patients with narcolepsy have difficulty in executing daily activities, socializing and maintaining personal relationships mainly due to cataplexy and EDS, and are estimated to experience a quality of life that is comparable or inferior to that of patients with epilepsy or sleep apnoea.[6,7]

Cataplexy has been identified in a range of species, including humans, horses, dogs and mice.[8,9] Genetic studies of cataplexy in dogs and mice indicate that loss of functional orexin or mutations in the genes encoding orexin receptors underlie the pathophysiology.[10–13] Humans with narcolepsy and cataplexy have a marked decrease in orexin levels in cerebrospinal fluid (CSF), together with a decreased number of orexin neurons in postmortem brain tissue.[2,14–16] The close associations of narcolepsy or cataplexy with *HLA-DQB1*06:02*, polymorphisms in the T-cell receptor α and *P2RY11* genes, and the pandemic anti-H1N1 vaccination, suggest that the loss of orexin neurons might have an autoimmune origin.[17–23]

This Review is timely because cataplexy is still an under-recognized symptom of narcolepsy—a disease that is currently underdiagnosed, especially in children. In Europe, the delay between the onset of symptoms and a correct diagnosis is about 10 years, due to insufficient awareness and understanding of the condition among clinicians and individuals.[24] Considering that the onset of narcolepsy is mainly in the second decade of life, and the condition can remain untreated for a further 10 years, many patients are affected during the most important period in their education and/or career. To overcome these consequences of narcolepsy and cataplexy, early diagnosis and treatment are essential to best improve patient quality of life.

Features of cataplexy

Cataplexy can be difficult to diagnose, as the symptoms vary not only between patients but also within

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Key points

- Cataplexy is the pathognomonic symptom of narcolepsy, and is characterized by sudden involuntary loss of skeletal muscle tone during wakefulness, typically triggered by strong positive emotions
- The pathogenesis of cataplexy in human narcolepsy involves degeneration of orexin neurons in the hypothalamus; genetically induced orexin deficiency causes cataplexy in both mice and dogs
- Cataplexy is thought to result from activation during wakefulness of the sleep circuitry involved in rapid eye movement sleep
- Reduced noradrenergic and increased inhibitory input to motor neurons causes muscle weakness or paralysis during cataplexy; positive emotions trigger cataplexy through neuronal pathways in the amygdala and medial prefrontal cortex
- γ-Hydroxybutyrate (GHB) and antidepressants are effective treatments for cataplexy, but most treatments (excluding GHB) are used 'off-label'
- Novel and experimental treatments to manage cataplexy are required, including orexin replacement therapy and immune-based therapies

individuals. For example, different cataplexy phenotypes exist in terms of age of onset, presenting symptoms (that is, the muscles affected), triggers (for example, laughter versus anger), frequency and severity, and the frequency of attacks often decreases with time.[4,25,26] Cataplectic attacks range from partial muscle weakness to complete paralysis, but are always bilateral, even if one side of the body is more affected than the other. These attacks are debilitating for patients because they leave the affected individual awake but either fully or partially paralyzed. Cataplexy affects all skeletal muscles apart from the diaphragm and extraocular muscles, but its greatest effect is on facial and neck muscles. Typically, the result is dysarthria, twitching of the facial muscles, jaw tremor, head dropping or jaw dropping, dropping of objects, and/or buckling of the knees (Supplementary Video 1 online). Extreme muscle weakness in the knees, arms and shoulders is also common. 50% of patients with cataplexy experience both partial muscle weakness and complete paralysis, whereas 30% experience only partial paralysis.[25,27] Injury during cataplexy is uncommon because most patients 'feel' the onset of muscle weakness and are able to sit or lie down. In rare instances, however, a cataplectic attack may result in fractures or bruises to the patient, and might be dangerous in certain settings (for example, during swimming).

During a cataplectic attack, patients remain conscious and are able to remember what happened to them before, during and after the cataplectic episode.[28] Some patients with narcolepsy report hypnagogic hallucinations during attacks, and some patients enter into REM sleep, but this is rare.[29] Skeletal muscle tone is reduced or absent during a cataplectic episode. A study of the neurophysiology of cataplexy indicates waxing and waning of postural muscle tone during cataplexy attacks that progresses along muscle groups rostro-caudally. Most episodes are accompanied by reduced heart rate and EEG desynchronization (Figure 1).[29,30]

The duration of an attack varies from several seconds to several minutes, and in rare instances it lasts for hours—a condition known as status cataplecticus.[2] The frequency of cataplectic attacks in patients varies from fewer than one episode per year to several episodes per day. Many patients with narcolepsy report that sleep loss and fatigue worsen the frequency of cataplectic attacks, but studies have not shown a clear link between sleep patterns (total sleep time, sleep efficiency, percentage of sleep stages, periodic leg movements and REM behaviour disorder), EDS and the severity of cataplexy.[31] Cataplexy persists throughout life, although the frequency of attacks might decrease with age.[31] Men often experience a higher number of cataplectic attacks than do women.[31]

Near the time of disease onset, children with narcolepsy often display abnormal motor behaviour that does not meet the classic definition of cataplexy.[31] Some children display a complex array of 'negative' (that is, hypotonic) and 'active' movements (for example, jaw opening with tongue protrusion, closure of eyelids and dyskinetic–dystonic movements) that can occur without any obvious emotional triggers.[32] These symptoms, however, decrease over a 3 year period and evolve into the classic cataplectic attacks described.[33]

In clinical practice, cataplexy is mostly diagnosed on the basis of the patient's history. Cataplexy is often documented in verbal reports, videos taken by the patient's family or, in some patients, after cataplectic episodes that occur in the presence of a physician. The clinical description of cataplectic attacks should be precise to enable classification as 'typical' or 'clear-cut', and should include triggering factors, muscles that are affected, duration and frequency of attacks. In patients with a potential differential diagnosis, the term 'atypical' cataplexy should be used and an assay of orexin levels in CSF used to verify the diagnosis of orexin deficiency or narcolepsy.

Trigger factors

In the International Classification of Sleep Disorders, narcolepsy is classified as type 1 or type 2.[34] According to this classification, type 1 narcolepsy (narcolepsy with cataplexy) is defined as EDS that persists for at least 3 months, plus at least two of the following: clear-cut cataplexy, a positive result on the Multiple Sleep Latency Test (that is, time elapsed from the start of a daytime nap period to the first signs of sleep of ≤8 min, and two or more sleep-onset REM periods) or low levels of orexin in CSF. Type 2 narcolepsy (narcolepsy without cataplexy, which as an entity remains controversial with unknown prevalence) is diagnosed as EDS that persists for at least 3 months and a positive result on the Multiple Sleep Latency Test, in the presence of normal levels of orexin. The presence of atypical cataplexy is sometimes reported in type 2 narcolepsy.

More than 90% of patients with narcolepsy and cataplexy present with low levels of orexin (<110 pg/ml) in CSF, which undoubtedly stem from the loss of approximately 90% of orexin-expressing neurons.[2,14,15] By contrast, more than 80% of individuals who are healthy or have atypical cataplexy have normal levels of orexin.[35] Importantly, a postmortem study of a patient who exhibited narcolepsy without cataplexy indicated loss of 33% of orexin-positive cells, largely in the posterior hypothalamus.[36] This finding suggests that narcolepsy with

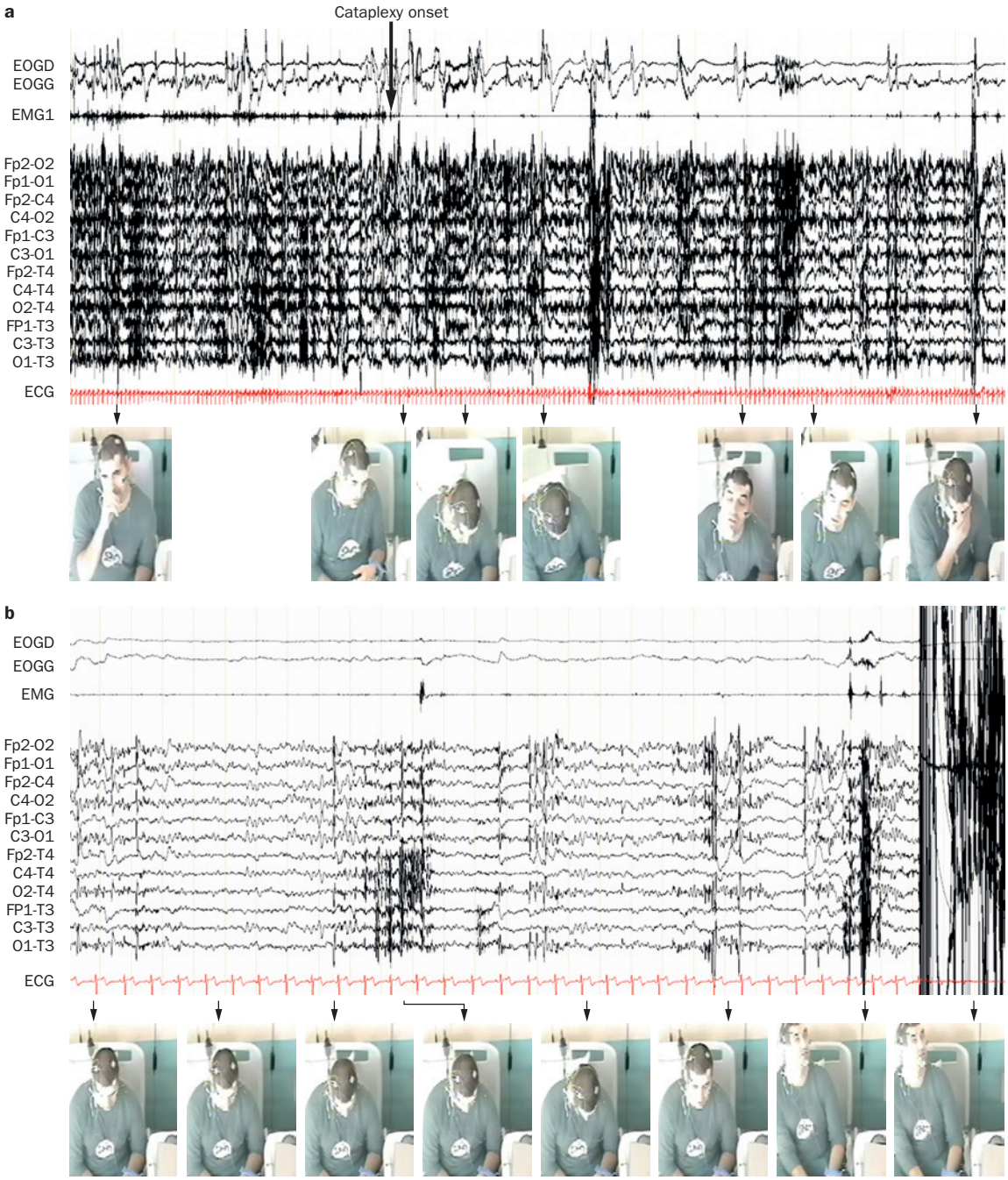

Figure 1 | Video-polysomnographic recording of a patient during a cataplectic attack with loss of muscle tone. Video clips were taken sequentially over a period of **a** | 2 min and **b** | 30 s. The patient presents with sustained loss of muscle tone that alternates with brief enhanced EMG activity leading to a flapping up-and-down motion of the body segments. These movements were reported as voluntary by the patient, who was trying to fight against the repetitive postural losses. The patient was fully conscious during the entire episode. Note that the EEG is characterized by low voltage frequencies (alpha and theta) and a decrease in heart rate during the brief suppressions of EMG activity. Abbreviations: ECG, electrocardiogram; EMG, electromyogram; EOGD, right electrooculogram; EOGG, left electrooculogram. Written consent for publication was obtained from the patient.

cataplexy only ensues when a patient loses almost all their orexin-positive cells.[14,15,36]

The association of H1N1 virus infection or anti-H1N1 vaccination with narcolepsy or narcolepsy with cataplexy is well-established.[21,23,37] For example, a substantial spike in newly diagnosed cases of narcolepsy or narcolepsy with cataplexy in children and adolescents who were exposed to the H1N1 virus or the vaccine has been recorded.[21,23,37] A study of patients with narcolepsy revealed the presence of $CD4^+$ T cells that were reactive to orexin and might also be reactive to a similar epitope on the H1N1 virus.[38] The presence of high titres

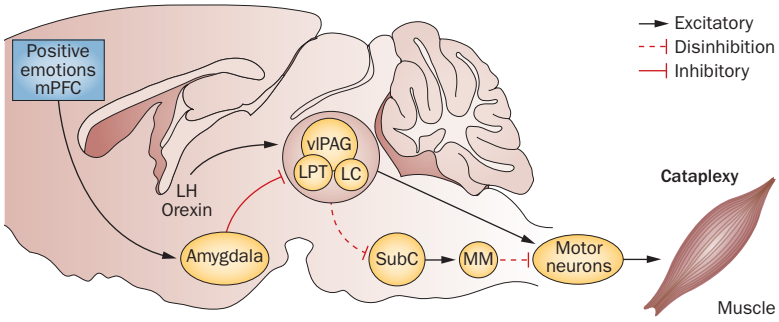

Figure 2 | Hypothetical circuits and pathways controlling cataplexy in the rodent brain. Activation during wakefulness of neural circuits involved in REM sleep paralysis is thought to underlie cataplexy, and is probably triggered by a two-part brainstem circuit—the SubC and MM connection. Glutamatergic neurons in the SubC trigger REM paralysis by activating GABAergic or glycinergic cells in the MM, which in turn project to and inhibit skeletal motor neurons. When a positive emotion is experienced, GABAergic neurons in the CeA switch on and inhibit cells in the LC, vlPAG and LPT. The LC–vlPAG–LPT circuit normally prevents muscle paralysis during wakefulness by suppressing the activity of SubC neurons. GABAergic CeA neurons inhibit neurons in the LC–vlPAG–LPT circuit, which in turn disinhibits the SubC to motor neuron circuit, triggering muscle paralysis and cataplexy. Muscle paralysis in cataplexy is also enabled by loss of noradrenergic input from LC neurons, which are inhibited during cataplexy. In healthy individuals, orexin-expressing neuronal activity cancels out the inhibitory effect of amygdalar neurons. Abbreviations: CeA, central amygdala; GABA, γ-aminobutyric acid; LC, locus coeruleus; LH, lateral hypothalamus; LPT, lateral pontine tegmentum; MM, medial medulla; mPFC, medial prefrontal cortex; REM, rapid eye movement; SubC, subcoereulus; vlPAG, ventrolateral periaqueductal grey.

of antibodies against streptolysin O and Tribbles homologue 2 (TRB-2, a protein that is abundant in orexin neurons) near the onset of narcolepsy also suggests an autoimmune basis for the disease and the potential for immunotherapy by generating crossreactive antibodies.[39,40] However, autoantibodies against TRB-2 in mice and other species might be a consequence rather than a cause of orexin neuron damage.

A link between cataplexy and emotion

A cataplectic attack is generally triggered by strong positive emotions such as excited laughter, repartee (for example, making a clever remark), elation, or surprise (for example, unexpectedly meeting a friend).[25] Infrequently, they are associated with negative emotions such as frustration or anger or, even more rarely, by stress, fear or physical effort.[2,25,41] Although a certain intensity of positive emotion is required to trigger a catapletic attack, nearly half of all patients experience spontaneous attacks that have no identifiable trigger.[25,32,42]

Benign muscle weakness, especially in the lower limbs, often occurs in healthy people when they laugh, hence the expression 'weak with laughter'.[43] This muscle weakness is linked to suppression of the Hoffmann reflex, which occurs during normal laughter in healthy individuals.[44] Orexin neurons are active in the response to strong emotions; therefore, loss of orexin-positive neurons in patients who have narcolepsy or narcolepsy with cataplexy hypothetically destabilizes the motor control system within the brainstem such that positive emotions trigger severe muscle weakness or total motor paralysis.[8,45]

Evidence exists that patients with cataplexy have altered neuronal responses to positive emotions. For example, neurophysiological data show that processing of humorous stimuli is temporally disturbed in patients with narcolepsy or narcolepsy and cataplexy.[46] Neuroimaging studies show that patients with narcolepsy have a reduced threshold for neuronal activation in the amygdala (a brain region that has a key role in the regulation of emotional activity) in response to both humorous and reward stimuli compared with controls.[47,48] In addition, functional neuroimaging studies describe changes in brain perfusion[49] and glucose metabolism[50] during cataplexy in humans. A PET study revealed increased metabolic activity during cataplexy in the bilateral precentral and postcentral gyri and primary somatosensory cortex, and a marked decrease in activity in the hypothalamus.[50] A study using single-photon emission CT indicated hyperperfusion in the right amygdala, bilateral cingulate gyri, basal ganglia, thalamus, premotor cortex, sensorimotor cortex, right insula, and brainstem, and hypoperfusion in the prefrontal cortex and occipital lobe, during cataplexy.[49,50] Abnormal functioning of the amygdala during cataplexy might stem from orexin deficiency, because the release of orexin from neurons is maximal when healthy individuals are experiencing positive emotions.[51] Animal studies also indicate that cataplexy is associated with abnormal function of the amygdala. Postmortem data show marked axonal degeneration in the amygdala of narcoleptic dogs, and electrophysiological recordings demonstrate that individual cells in the amygdala have increased firing rates during cataplexy.[52,53]

Animal models

Genetic studies in narcoleptic dogs and mice have provided valuable insights into the pathophysiology of cataplexy. Genetic deletion of *Hcrt*, which encodes orexin, in mice and the consequent degeneration of orexin-expressing neurons induces a behavioural phenotype that recapitulates the cardinal features of human narcolepsy, including cataplexy, sleepiness and disturbed REM sleep.[10,11,13] In dogs, introduction of exon skipping into the *Hcrt-R2* gene causes a narcoleptic phenotype, including cataplexy.[12,53] These findings not only corroborate human data showing that narcolepsy or narcolepsy and cataplexy is the result of abnormal functioning of the orexin system (Figure 2), but also suggest that the orexin system is important in promoting arousal, controlling REM sleep, and regulating postural muscle tone.[45,53]

Cataplectic attacks in $Hcrt^{-/-}$ mice seem remarkably similar to those in human cataplexy (Table 1). Attacks are characterized by the rapid onset of skeletal muscle paralysis during wakefulness, resulting in abrupt postural collapse that terminates purposeful behaviour (Supplementary Video 2 online).[8] Mice seem to be awake during attacks, because they respond to visual stimuli, and their EEG activity is similar to the spectrum of waking EEG activity seen during cataplectic episodes in children.[13,54] Most cataplectic attacks in $Hcrt^{-/-}$ mice range from 15 s to 2 min, with a mean duration of about

Table 1 | Cataplexy in humans and animal models

Features	Human	Mouse*	Dog‡
Behavioural	Postural collapse, jaw sagging, weak knees	Postural collapse, falling prone or onto their sides	Postural collapse, weakness
Level of consciousness	Awake (memory of episode)	Probably awake (response to visual stimuli intact)	Awake (response to visual stimuli intact)
Triggers	Strong positive emotions (for example, laughter, joking, elation)	Emotionally rewarding behaviours (for example, eating palatable food, running, social interaction)	Emotionally rewarding behaviours (for example, eating palatable food, running, social interaction)
Duration of cataplectic attach	Brief (seconds to minutes)	Brief (seconds to minutes)	Brief (seconds to minutes)
Cortical EEG	Mixture of waking and REM-sleep-like EEG	Mixture of waking and REM-sleep-like EEG	Mixture of waking and REM-sleep-like EEG
Muscle tone	Muscle paralysis or weakness; loss of EMG activity	Muscle paralysis; loss of EMG activity	Muscle paralysis; loss of EMG activity
Therapy	Suppressed by monoamine reuptake blockers (for example, antidepressants) and GHB	Suppressed by monoamine reuptake blockers (for example, antidepressants) and GHB	Suppressed by monoamine reuptake blockers (for example, antidepressants) but no response to GHB

*$Hcrt^{-/-}$ mouse model. ‡Disruption of *Hcrtr2*. Abbreviations: EMG, electromyogram; GHB, γ-hydroxybutyrate; REM, rapid eye movement.

60 s, similar to human cataplexy. Cataplectic attacks end with rapid restoration of muscle tone and resumption of normal waking behaviour, as they do in patients with narcolepsy.

As in humans with narcolepsy, cataplectic attacks in narcoleptic dogs and mice can be triggered by positive emotional stimuli. In narcoleptic dogs, cataplexy is triggered by palatable foods, play or sex, and in narcoleptic mice it is triggered by reward stimuli such as social reunion, running in wheels and palatable food (Supplementary Video 3 online).[55,56] The frequency of cataplectic attacks is significantly increased when $Hcrt^{-/-}$ mice are given access to running wheels and chocolate, which are both reward stimuli for mice.[41,57] EEG recordings in narcoleptic mice show that cataplexy begins with a brief phase of wakefulness, followed by high-amplitude irregular theta activity and then by short 1–2 s bursts of high-amplitude, regular (~7 Hz), hypersynchronous paroxysmal theta activity.[54] Intracranial EEG recordings also show that this activity involves the medial prefrontal cortex, a region associated with reward-driven motor impulses.[54] Interestingly, hypersynchronous paroxysmal theta activity (~4 Hz) is also observed at the onset of cataplexy in children with narcolepsy. These bursts of activity might represent medial prefrontal cortical activity, but the clinical relevance of this finding is unclear.[54]

Neurobiology

A longstanding hypothesis in sleep medicine is that cataplexy results from the intrusion of REM sleep paralysis into wakefulness.[2,4,58] This idea stems from the observation that cataplexy and REM sleep paralysis have a common neural mechanism.[59] For example, tricyclic antidepressants , which are used to alleviate cataplexy, also suppress REM sleep, and rapid withdrawal of these drugs causes a rebound of either cataplexy or REM sleep.[2,60] Deep tendon and monosynaptic Hoffmann reflex activity are absent during both cataplexy and REM sleep.[2,4,44] Neuroimaging studies of patients with narcolepsy and electrophysiological recordings from isolated cells in narcoleptic dogs show that the brainstem circuitry involved in REM sleep might have similar activity during both REM sleep and cataplectic episodes.[49,52] The underlying cause of clinical cataplexy is a reduction in skeletal motor neuron activity, which results from increased inhibitory and reduced excitatory signalling in the brain.[41,58] Inhibitory signals are produced by γ-aminobutyric acid-releasing (GABAergic) and glycinergic neurons in the medial medulla, which are intensely activated during cataplexy and REM sleep, but not during normal waking.[55,61,62] Simultaneously, pontine grey neurons, which are responsible for atonia both in cataplexy and in REM sleep, activate GABAergic neurons, which in turn inhibit noradrenergic neurons in the locus coeruleus (Figure 2).[63] The cessation of firing of noradrenergic neurons stops the release of noradrenaline to motor neurons and results in their disfacilitation.[8] The two processes cause reduced motor neuron activity and a decrease in, or elimination of, tone in the postural muscles (Figure 2).[58,64]

The close association between the occurrence of cataplexy and orexin deficiency in patients with narcolepsy and animal models of narcolepsy suggests that orexin has a key role in the pathophysiology of cataplexy.[2] The strength of the excitatory projections from orexin neurons to the noradrenergic neurons in the locus coeruleus is thought to prevent cataplexy in healthy individuals.[65,66] In patients with narcolepsy or narcolepsy and cataplexy, however, orexin deficiency reduces normal levels of noradrenergic neuronal activity, which closely correlates with cataplectic attacks in $Hcrt^{-/-}$ mice, and dogs with narcolepsy.[8,66] Drugs that increase noradrenaline levels in the CNS are effective in alleviating cataplexy in humans, dogs and mice.[8,26,65] A study demonstrated that the frequency of cataplectic attacks was reduced when orexin receptors were restored to serotonergic neurons in the dorsal raphe of mice lacking orexin receptors, which suggests the serotonin signalling system

could also be involved in cataplexy.[67] Previous work has shown that activity of serotonergic neurons in the dorsal raphe does not change during cataplexy, in contrast to noradrenergic neurons in the locus coeruleus.[65,68]

Orexin A and orexin B are two different peptides produced by 70,000–80,000 neurons in the healthy hypothalamus in humans. Orexin neurons not only strongly innervate and directly excite noradrenergic, dopaminergic, serotonergic, histaminergic and cholinergic neurons, but also modulate the release of glutamate and other amino acid transmitters.[69,70] Behavioural studies revealed that orexin is released at high levels during active waking, at intermediate or low levels in quiet but alert waking periods and during REM sleep, and at minimal levels in non-REM sleep.[71,72] Electrophysiological recording of neuronal unit activity in narcoleptic dogs shows that most of the brain regions involved in the generation of REM sleep atonia are also involved in episodes of cataplexy.[52,55,68,73] Thus, at the neuronal level, these findings support the concept of cataplexy as an intrusion of REM sleep paralysis into wakefulness. Cataplexy is not identical to REM sleep, however, the main difference being the maintenance of consciousness. Preservation of activity of histaminergic neurons during cataplexy but not in REM sleep suggests a function for histamine in maintaining wakefulness during cataplectic episodes.[66] Orexin neuron activity and orexin release are absent during conditions of quiet waking and drowsiness, but the cessation of this neuronal activity is not sufficient enough to cause cataplexy under normal physiological conditions; thus, the absence of orexin neurons in narcolepsy or narcolepsy and cataplexy might be associated with other anatomical and physiological changes in the brain, perhaps secondary to orexin malfunction.[74–76] Accordingly, two studies of histaminergic neurons in human narcolepsy or narcolepsy and cataplexy indicated an increase in numbers of these neurons, but this result differs from results in animal models.[77,78] The relationship between changes in histaminergic neuronal numbers, cataplexy and other symptoms of narcolepsy across different species is unclear.

The amygdala has an important role in the processing of emotional stimuli[79] and, therefore, might also be important in triggering cataplexy. Clinical and basic research studies show that changes in neuronal activity in the amygdala are associated with cataplexy. Functional neuroimaging shows increased activity in the amygdala while patients watch humorous photographic images, and electrophysiological recordings from isolated cells in narcoleptic dogs demonstrate that activity of certain amygdalar neurons is closely associated with cataplectic attacks.[52,80] Another study indicates that bilateral lesions of the amygdala significantly reduce the frequency of cataplectic attacks in *Hcrt*$^{-/-}$ mice.[41] A population of GABAergic neurons in the amygdala innervates the locus coeruleus, lateral pontine tegmentum (LPT) and ventrolateral periaqueductal grey (vlPAG), the functions of which are to support muscle tone during wakefulness.[41] Lesions in the LPT and vlPAG in rodents cause sporadic bouts of muscle paralysis during wakefulness that resemble cataplectic attacks, and inactivity of locus coeruleus neurons is associated with muscle atonia during cataplexy.[8,66,81,82] In patients experiencing positive emotions, therefore, GABAergic neurons in the amygdala might become active and in turn inhibit the activity of cells in the locus coeruleus, LPT and vlPAG that would normally maintain waking postural tone.

The medial prefrontal cortex (mPFC) also has a role in triggering cataplexy. Ingestion of palatable foods (for example, chocolate), which trigger cataplexy in *Hcrt*$^{-/-}$ mice, also activates neurons in the mPFC, and inhibition of mPFC neurons markedly reduces cataplectic attacks associated with positive emotional stimuli.[83] In addition, neurons in the mPFC innervate the amygdala and lateral hypothalamus, which contain neurons that are active during cataplexy and might innervate brainstem regions involved in the regulation of muscle tone.

Treatment

The inhibitory effect of various antidepressants on the adrenergic system is supported by *in vivo* and *in vitro* studies.[84] The dopaminergic system is involved in the regulation of cataplexy via the D2-like receptor in mouse models of narcolepsy. The frequency of cataplectic attacks in these mice increases after D2-like receptor activation, and decreases after receptor blockade.[85] Cholinergic systems are also thought to be important in the regulation of cataplexy in animal models, with stimulation of the cholinergic system severely aggravating canine cataplexy.[86]

The effectiveness of drugs used to treat cataplexy is difficult to evaluate, as the methods employed to assess the frequency and intensity of attacks—for example, recall history, scale, diaries or video recordings—vary from one study to another. Some patients might exhibit a decrease in frequency and severity of cataplectic attacks with disease duration. Behavioural measures such as cognitive behavioural therapy might be of interest for some patients to enable them to either control their emotion or learn to avoid situations that trigger cataplectic attacks, but this approach is not usually sufficiently effective to be considered as a recommended treatment.

Antidepressants

Antidepressants and γ-hydroxybutyrate (GHB, also known as sodium oxybate) are reportedly the most effective drugs to treat cataplexy (Table 2).[87] Neither tricyclic agents nor selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs) are approved by the European Medicines Agency or the FDA for the treatment of cataplexy in children or adults. This practice is based only on expert opinion, as no studies demonstrating efficacy and safety of these drugs for this indication have been carried out.

Tricyclic agents, which were the first drugs used to treat cataplexy,[87,88] are nonspecific monoamine reuptake inhibitors that increase the availability of serotonin, noradrenaline and, in some cases, dopamine.[88] Some tricyclic agents also have anticholinergic properties,

which might contribute to their anticataplectic effect. Clomipramine is the most widely used tricyclic agent to treat cataplexy.[87] Often, these agents have an effect on cataplexy within 48 h at doses below those required to treat depression, but tolerance frequently develops. Cataplexy rebound, or status cataplecticus, which is defined by an increase in the number of attacks and the severity of cataplexy, typically occurs if antidepressant intake, especially tricyclic agents, is interrupted or abruptly halted.

Monoamine oxidase inhibitors (MAOIs) increase the availability of the monoamine neurotransmitters, for example, dopamine, noradrenaline and serotonin. Studies have indicated that MAOIs (specifically, selegiline hydrochloride) strongly suppress REM sleep and reduce the frequency of cataplectic attacks, but these drugs are now rarely used because they are associated with serious adverse effects.[87]

SSRIs (fluoxetine, paroxetine and citalopram), although less effective than tricyclic antidepressants in decreasing the frequency of cataplectic attacks, are widely used for this purpose, and the frequency of associated adverse effects is lower than for tricyclic agents. SSRIs, and SNRIs (such as venlafaxine, duloxetine and milnacipran), are the antidepressants most widely used to treat cataplexy, particularly venlafaxine as it is effective within 48 h.[87] Due to the short duration of action of venlafaxine, the extended-release form seems to be preferable, starting at a low dose (37.5 mg) but higher doses are often needed (75–300 mg). Venlafaxine is not recommended for treatment in pregnant women with narcolepsy, but has an acceptable tolerance profile for use in children.[89,90] The differential efficacy of venlafaxine on either 'negative' (hypotonia) or 'active' motor components during cataplexy is unknown. Other SNRIs, such as duloxetine and milnacipran, or noradrenaline reuptake inhibitors, such as viloxazine, reboxetine, atomoxetine and bupropion, seem to be promising treatments in decreasing the frequency of cataplectic attacks, are well tolerated, and have a mild stimulant effect.[91,92]

Table 2 | Therapies for cataplexy

Mode of action	Treatment	Dose
First line		
$GABA_B$ agonist that modulates dopamine neurotransmission	GHB	6–9 g per night*
Norepinephrine and serotonin reuptake inhibitor	Venlafaxine	37.5–300.0 mg per day
Selective serotonin reuptake inhibitors	Fluoxetine Citalopram	20–60 g per day 20–40 mg per day
Tricyclic antidepressants	Clomipramine Protriptyline	10–20 mg per day 5–10 mg per day
Second line		
Tricyclic antidepressants	Clomipramine Protriptyline	30–100 mg per day 20–80 mg per day
Norepinephrine and serotonin reuptake inhibitor	Duloxetine	30–120 mg per day
Norepinephrine reuptake inhibitors	Reboxetine Atomoxetine	2–10 mg per day 2–10 mg per day
Third line		
Tricyclic, anorectic, nonamphetamine stimulant	Mazindol	1–4 mg per day
Monoamine oxidase inhibitor	Selegiline	20–40 mg per day
Future therapies		
$GABA_B$ agonist	GHB slow-release	6–9 g per night*
NA	Immune-based therapy at disease onset	Intravenous immunoglobulin, plasmapheresis or monoclonal antibodies
NA	Orexin, orexin agonists or orexin-expressing cell transplantation	NA

*GHB is the first and only medication indicated for cataplexy. Abbreviations: $GABA_B$, γ-aminobutyric acid type B receptor; GHB, γ-hydroxybutyrate; NA, not applicable.

γ-Hydroxybutyrate

GHB is a natural metabolite of γ-aminobutyrate and functions as a neurotransmitter at the GHB receptor (GHBR; also known as solute carrier family 52, riboflavin transporter, member 2) at physiological concentrations and as a GABA receptor agonist at pharmacological concentrations, and also modulates dopaminergic signalling.[93]

GHB is effective at reducing both the frequency and intensity of cataplectic attacks, as well as restoring nocturnal sleep continuity and reducing EDS in patients with narcolepsy or narcolepsy and cataplexy.[93–95] Despite a half-life of only 40–60 min, its clinical benefit persists well beyond this period, and with nightly use the benefit is significant after 4 weeks, highest after 8 weeks, and maintained during long-term therapy.[94,95] GHB also has an acceptable tolerance profile for treatment of children; however, as for venlafaxine, its relative efficacy on negative versus active components of cataplexy is unknown.[89] It can also be used with antidepressant or stimulant therapy, but should not be used in conjunction with alcohol.[95] Unlike antidepressants, interruption of treatment with GHB does not result in a rebound of cataplexy. One major issue with the use of GHB is its nonmedical use, as it is sometimes used in athletes for performance enhancement owing to its metabolic effects. Safety data and clinical experience of GHB therapy indicate that the potential for misuse is low in patients with narcolepsy.[95,96,97]

Effects of stimulants

Drugs that increase adrenergic and dopaminergic signalling, such as amphetamines, methylphenidate hydrochloride and mazindol (but not modafinil), also decrease the frequency of cataplectic attacks. Although rarely used in practice, mazindol is a tricyclic, anorectic, nonamphetamine that is a very effective stimulant (half-life 10 h) and is also effective in the treatment of cataplexy.[95] A careful cardiological follow-up is required

with mazindol and amphetamines. Mazindol has less potential for misuse and development of tolerance than amphetamines in patients with narcolepsy.

Future therapeutic management

Orexin deficiency underlies the pathophysiology of cataplexy; therefore, orexin replacement therapy could be an effective strategy. In humans, the use of orexin-based treatment has been disappointing; however, there has been some success with this approach in treating cataplexy in dogs.[98,99] Intraventricular delivery of orexin A has potential efficacy, but is probably inappropriate for long-term therapy. Intranasal delivery to bypass the blood–brain barrier is a noninvasive method to deliver orexin to the brain. This method has been shown to improve cognition and olfactory performance and stabilize sleep in rhesus monkeys and patients with narcolepsy or narcolepsy and cataplexy, but has not been tested for its effects on cataplexy alone.[100–103] Synthetic orexin receptor agonists might be another treatment option. Transplantation of orexin neurons might, theoretically, provide a cure for patients with narcolepsy, even if the results of neuronal transplantation in other diseases have been disappointing, with graft rejection and low survival rates of the implant.[104,105]

The activation of histaminergic neurons by an inverse agonist of the histamine H3 receptor, which is presynaptic and enhances histamine release, is a promising therapy. One of these compounds, pitolisant, improved wakefulness in normal animals, blocked abnormal transition from wakefulness to REM sleep in *Hcrt*$^{-/-}$ mice, and decreased sleepiness and might have the potential to treat cataplectic attacks in patients with narcolepsy.[106,107]

Finally, on the basis of the immune-mediated hypothesis for the loss of orexin neurons, we suggest that immunotherapies at disease onset might modify the long-term disease outcome if the 'autoimmune' process that targets orexin neurons is not too advanced and can be partially reversed. Corticosteroids, intravenous immunoglobulin, plasmapheresis, immunoadsorption and alemtuzumab have all been tested in the treatment of cataplexy, with variable efficacy.[108–112] In one patient who had undetectable levels of orexin in the CSF, intravenous immunoglobulin treatment only 15 days after disease onset resulted in clinical improvement of cataplexy and biological normalization of CSF orexin A levels.[113] At the onset of narcolepsy, high doses of immunomodulators might downregulate T-cell functions and pathogenic cytokines and interfere with autoantigen recognition through *HLA-DQB1*06:02* expression during induction therapy.[114] Well-designed trials of immunotherapies in patients at the onset of disease are needed; however, an improved understanding of the pathophysiology of orexin neuron loss is also required to develop effective treatment strategies.

Conclusions

Cataplexy is the pathognomonic symptom of narcolepsy, but is underdiagnosed as a symptom as it varies phenotypically in terms of age of onset, affected muscle group, trigger factors, frequency and intensity. Cataplexy results from the inappropriate activation during wakefulness of the brainstem circuits that normally generate muscle atonia during REM sleep. The pathological intrusion of REM sleep paralysis into wakefulness occurs almost exclusively when orexin neurons are depleted. Neurons expressing orexin normally serve to drive and synchronize the activity of monoaminergic and cholinergic neuronal systems. The loss of an excitatory noradrenergic drive onto motor neurons underlies the loss of postural muscle tone during cataplexy. Involvement of the amygdala and medial prefrontal cortex is highlighted by the triggering of cataplectic attacks by emotional stimuli and processing thereof.

To overcome the consequences of narcolepsy and cataplexy, early diagnosis and treatment of patients are essential. Despite a major advance in our understanding of the neurobiology of narcolepsy–cataplexy, there is no cure. Current therapeutic management is only symptomatic, with widespread use of antidepressants and GHB to reduce the frequency of cataplectic attacks. The discovery of orexin deficiency in humans has led to a new diagnostic test for narcolepsy and might lead to orexin replacement therapy. Future therapeutic targets must be focused on immunotherapies at early stages in the disease to prevent the loss of orexin neurons and disease progression.

Review criteria

Articles were identified from publications listed in English on PubMed from January 1970 to October 2013. The following keywords were used alone and in combination: "narcolepsy", "cataplexy", "REM sleep", "atonia", "motoneuron", "amygdala", "emotions", "hypocretin", "orexin", "dog", "mouse", "mice", "brainstem", "locus coeruleus", "noradrenergic", "arousal" and "neurobiology". Publications were also identified through the authors' collections of scientific literature.

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Author contributions

Y.D. researched data for the article. Y.D., J.M.S. and J.H.P. wrote the article and substantially contributed to discussion of the content. Y.D., J.M.S., R.L., Z.A.T. and J.H.P. reviewed and/or edited the manuscript before submission.

Supplementary information is linked to the online version of the paper at www.nature.com/nrneurol.