

PATHOPHYSIOLOGICAL AND PHARMACOLOGIC ASPECTS OF THE SLEEP DISORDER NARCOLEPSY

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Narcolepsy is frequently both over- and under-diagnosed. The condition is not rare and has population prevalence similar to that of multiple sclerosis (57,78,141). Studies have demonstrated a large psychosocial impact of the disease (22,23). Narcolepsy is also a unique disease model for basic sleep researchers with the availability of validated animal models and as the only known disorder with a complete disorganization of sleep and REM sleep. Our understanding of the pathophysiology of the disorder is rapidly emerging, thanks to the discovery that narcolepsy-cataplexy is associated with a deficiency in the hypocretin (Orexin) neuropeptide system (30,68,106). The fact that human narcolepsy is HLA-associated (59,82) also suggests a possible autoimmune mediation in many cases. In this chapter, we briefly outline how narcolepsy is diagnosed and treated, as well as discuss future directions for this rapidly evolving area.

CLINICAL AND EPIDEMIOLOGIC ASPECTS OF HUMAN NARCOLEPSY

Cataplexy: A Pathognomonic Symptom of the Narcolepsy Syndrome

Patients with narcolepsy experience brief episodes of muscle weakness when laughing, angry, or elated, a symptom referred to as cataplexy (3,7,46,55,114). These episodes most often affect the legs or the face, leading to knee buckling, sagging of the jaw, slurring of speech, and/or dropping of the head (7,46,55). Episodes are brief (a few seconds to several minutes at most), bilateral, and rarely lead to body collapse and/or long-lasting episodes of complete paralysis. Consciousness is preserved during cataplexy (7,46,55).

The importance of carefully defining cataplexy should

be emphasized. Epidemiologic studies have shown that up to 30% of the general population experiences “muscle weakness episodes in reaction to emotions” (4,7,57). Clearly, this definition is not sufficient to establish cataplexy. Genuine cataplectic episodes in narcolepsy are triggered by very specific emotions. Joking, laughing, and anger are the most reliable triggering events (7). Rare episodes of muscle weakness occurring exclusively in the context of unusual emotional triggers, for example while tense or stressed, or during sexual or athletic activities, should not be considered as cataplexy (7).

The presence of cataplexy being critical to the diagnosis, it is clinically useful to differentiate definite/clear-cut cataplexy from doubtful, possible cataplexy (very rare events, long duration, and unusual triggers). For many clinicians, the presence of clear-cut cataplexy is sufficient to diagnose narcolepsy and narcolepsy-cataplexy is etiologically homogeneous. In favor of this hypothesis, almost all (85% to 100%) patients with definite cataplexy share a specific genetic marker, HLA-DQB1*0602, across various ethnic groups (81). This high association contrasts with DQB1*0602 control frequencies ranging from 12% in Japanese, to 20% to 25% in most white populations, and 38% in African Americans (69,81).

Other Narcolepsy Symptoms

Although cataplexy is the most specific symptom of narcolepsy, it is frequently mild and rarely the most significant problem clinically for narcoleptic patients. Rather, persistent daytime sleepiness is the most disabling symptom in most patients. Patients with narcolepsy experience a permanent background of daytime sleepiness culminating in overwhelming sleep attacks (3,55,104,114). Narcoleptic subjects may continue their activity during these sleep attacks in a semiautomatic manner, without any memory of the event (automatic behavior). Daytime napping usually relieves daytime sleepiness temporarily (55). Other symptoms

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frequently reported include sleep paralysis, an inability to move occurring at sleep/wake transitions, and hypnagogic hallucinations, dreamlike experiences at sleep onset (3,55,104,114). These symptoms are also not specific to narcolepsy and are frequently observed in the general population and patients with other sleep disorders (4,7,109,110). Patients with narcolepsy also have frequently disturbed nocturnal sleep (3,55,104,114). Nightmares, REM behavior disorder, and periodic leg movements during sleep are commonly observed (56,104,135). Typically, patients with narcolepsy fall asleep easily and wake up after a few hours, unable to fall asleep again at night (3,55,104,114).

Diagnosis of Narcolepsy

The diagnosis of narcolepsy is primarily clinical but polysomnographic studies are useful to document a sleep abnormality and to exclude confounding and/or associated sleep disorders. These tests are also useful to justify future treatment using amphetamine-like stimulants. Most commonly, nocturnal polysomnography with monitoring of breathing and oxygen saturation is carried out to exclude sleep apnea syndrome or other problems potentially disrupting nocturnal sleep. This is followed by a four- to five- nap multiple sleep latency test (MSLT) (4,29). These tests must be carried out without any psychotropic treatment and after adequate washout periods (at least 2 weeks for antidepressants, because of their strong REM sleep effects). Sleep logs are used to document adequate nocturnal sleep amount prior to testing. Nocturnal polysomnography in patients with narcolepsy usually reveals a short REM latency in less than 20 minutes (50% of the cases), low sleep efficiency (associated insomnia), and frequently associated periodic leg movements (56). MSLT data indicates short mean sleep latency ($SL \leq 8$ minutes) and REM episodes (2 or more sleep onset REM periods, or SOREMPs), a result generally considered diagnostic of narcolepsy (4) (Table 131.1).

Epidemiologic Studies of Narcolepsy-Cataplexy

Epidemiologic studies have only been performed for narcolepsy-cataplexy. Hublin and associates performed the best-designed study in Finland (57). Using a twin registry and systematic evaluation of 10,000 twin individuals, this study led to a prevalence of .023%. Other studies have led to very similar prevalence values (.02% to .05%) in North American and various other Western European countries (78). Population-based studies suggest a higher prevalence for narcolepsy-cataplexy in Japan (.16% to .17%), but diagnostic criteria did not require polysomnography to verify the diagnosis (54,150). Studies comparing sleep disorder populations in a sleep disorder center in Israel suggest a low prevalence (.002%) for the syndrome in this population (65).

TABLE 131.1. INTERNATIONAL CLASSIFICATION OF SLEEP DISORDERS (ICSD) DIAGNOSTIC CRITERIA FOR NARCOLEPSY

Diagnostic Criteria: Narcolepsy

- A. A complaint of excessive sleepiness or sudden muscle weakness
- B. Recurrent daytime naps or lapses into sleep that occur almost daily for at least 3 months
- C. Sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy)
- D. Associated features include:
 1. Sleep paralysis
 2. Hypnagogic hallucinations
 3. Automatic behaviors
 4. Disrupted major sleep episode
- E. Polysomnography demonstrates one or more of the following:
 1. Sleep latency less than 10 minutes
 2. REM sleep latency less than 20 minutes and
 3. An MSLT that demonstrates a mean sleep latency of less than 5 minutes
 4. Two or more sleep onset REM periods
- F. HLA typing demonstrates DR2 positively
- G. Absence of any medical or psychiatric disorder that could account for the symptoms
- H. Other sleep disorders may be present but are not the primary cause of the symptoms (e.g., periodic limb movement disorder or central sleep apnea syndrome)

Minimal Criteria: B + C, or A + D + E + G

From American Sleep Disorders Association. ICSD-International Classification of Sleep Disorders diagnostic and coding manual. Rochester, MN. American Sleep Disorders Association, 1991.

Narcolepsy without Cataplexy and Disease Spectrum

In current patient populations, only 50% to 80% of narcoleptic patients have cataplexy. The presence of cataplexy is not necessary to diagnose narcolepsy based on current international diagnostic criteria. Rather, narcolepsy is either diagnosed: (a) in the presence of cataplexy with or without results from associated sleep tests; or (b) without cataplexy but with abnormal MSLT results, associated sleep paralysis or hypnagogic hallucinations and after excluding other sleep disorders (e.g., abnormal breathing during sleep) (4). The rationale for a broader definition of narcolepsy stems from the observation that sleep paralysis, hypnagogic hallucinations, and SOREMPs are all pathologic manifestations of abnormal REM sleep in narcolepsy (52,123).

Whereas the prevalence of narcolepsy-cataplexy is well established, the population prevalence of narcolepsy without cataplexy is unknown and could be as high as several percent of the population. Genetic studies indicate a higher HLA association in narcolepsy-cataplexy (85% to 100% DQB1*0602 positive) versus narcolepsy without cataplexy (40% DQB1*0602 positive) (80), suggesting increased etiologic heterogeneity in narcolepsy without cataplexy.

GENETIC PREDISPOSITION IN HUMAN NARCOLEPSY

The genetic aspects of human narcolepsy are complex. Since 1983–1984, human narcolepsy has been known to be associated with HLA-DR2 (59); more recent results suggest a primary association with HLA-DQ (76,82,96,117), with HLA DQB1*0602 playing a primary role in disease predisposition and other HLA alleles having secondary effects (88). The importance of environmental factors is indicated by the low degree of concordance of monozygotic twins (25% to 31%) (78). Genuine multiplex families are rare; most narcoleptic patients do not have a family history. Only 1% to 2% of first-degree relatives of narcolepsy patients ever develop narcolepsy-cataplexy (20,44,78). One to two percent affected in first-degree relatives indicates a 20- to 40-fold increased risk that cannot be explained by HLA-associated genetic factors alone (78). Further, multiplex families are more frequently HLA-DQB1*0602 negative than sporadic cases, suggesting the importance of non-HLA genetic factors (83).

The HLA association observed in narcolepsy suggests a primary involvement of the immune system in the pathophysiology of the disorder, yet all studies aiming at demonstrating an autoimmune mediation have failed (28,77,86). The recent discovery that narcolepsy is associated with undetectable CSF hypocretin-1 levels (106) suggests that this hypothesis should be revisited now that a potential target cell population has been identified.

ANIMALS MODELS OF NARCOLEPSY AND HYPOCRETIN (OREXIN)

In 1973 and 1974, narcolepsy was first reported in a dachshund and a poodle (60,91). Autosomal recessive occurrence of narcolepsy in doberman pinschers and Labrador retrievers was subsequently discovered, and a colony of genetically narcoleptic Dobermans and Labradors was established at Stanford University (13). As with human patients, narcoleptic animals exhibit muscle weakness (cataplexy) when emotionally stimulated. Polygraphic studies in narcoleptic dogs have also demonstrated that narcoleptic canines have a shorter latency to drowsiness, light sleep, and REM sleep than do control animals (104). Sleep paralysis and hypnagogic hallucinations may also exist in narcoleptic dogs, but are impossible to document owing to their subjective nature.

In narcoleptic Dobermans and Labradors, the major susceptibility gene, *canarc-1*, is unlinked to dog leukocyte antigen (DLA) (87). Linkage analysis with various genetic markers, including minisatellite probes and functional candidate gene probes, revealed that the canine narcolepsy gene cosegregated with a polymorphic band cross-reacting with the switch region of the human immunoglobulin μ heavy-chain gene (87). After 10 years of chromosome walking in dogs,

the canine narcolepsy gene was finally identified as the hypocretin receptor 2 gene (*Hcrtr2*) (68). Three mutations causing loss of function of *Hcrtr2* and impaired postsynaptic hypocretin neurotransmission were identified in Labradors, dachshunds, and Dobermans, respectively (68). The discovery of *canarc-1* (*Hcrtr-2*) was followed by the report that preprohypocretin (prepro-Orexin) knockout mice also exhibit a narcolepsy-like phenotype, shorter REM sleep onset, and episodes of behavioral arrest similar to cataplexy in canine narcolepsy (30). Deficits of either the hypocretin ligand or its receptor-2-mediated transmission thus generate narcolepsy in animal models.

Following up on this discovery, hypocretin 1-peptide (Orexin A) levels were measured in the cerebrospinal fluid (CSF) of narcoleptic humans. Strikingly, *Hcrtr1* was below detectable levels in seven out of nine patients, in contrast to eight control subjects who all had normal *Hcrtr1* levels (106). These results suggest that a deficit in hypocretin transmission is also involved in cases of human narcolepsy, although disease heterogeneity may exist (106). (See more details in monoaminergic cholinergic imbalance and deficit in hypocretin neurotransmission sections.)

TREATMENT OF HUMAN NARCOLEPSY

Pharmacologic Treatment of Daytime Sleepiness with Amphetamine-like Compounds

Nonpharmacologic treatments (i.e., behavioral modification such as regular napping and work accommodations) are often helpful (128,129), but are rarely sufficient to control the symptoms. Referral to patient support groups (e.g., narcolepsy network) and giving directives regarding driving and other potentially dangerous activities is critical until a better understanding and control of the disorder by the patient is achieved. In a recent survey by a patient group organization (8), 94% of all patients reported using pharmacologic therapies, mostly stimulant medications. Sleepiness is usually treated using amphetamine-like CNS stimulants or modafinil, a novel wake-promoting compound unrelated to the amphetamines (Table 131.2). The most commonly used amphetamine-like compounds are methamphetamine, *d*-amphetamine, methylphenidate, pemoline, and mazindol (Table 131.2). The most important pharmacologic property of amphetamine-like stimulants is to release catecholamines, mostly dopamine and norepinephrine (62,147). Monoamine reuptake blockade and MAO inhibition also occur at high doses and the importance of these secondary pharmacologic effects varies from one amphetamine derivative to another (73). Pharmacologic studies using the canine narcolepsy model strongly suggest that presynaptic enhancements of dopamine transmission contribute to the EEG arousal effects of amphetamine-like CNS stimulants and modafinil (103). (See also the Canine Narcolepsy section.)

TABLE 131.2. COMMONLY USED TREATMENTS FOR EXCESSIVE DAYTIME SLEEPINESS (EDS)

Stimulant Compound	Usual Daily Doses ^a	Half-Life (Hours)	Side Effects/Notes
Sympathomimetic stimulants			
<i>D</i> -Amphetamine sulfate ^b	5–60 mg (15–100 mg)	10–12	Irritability, mood changes, (urinary pH-dependent) headaches, palpitations, tremors, excessive sweating, insomnia
Methamphetamine HCl ^b	5–60 mg (15–80 mg)	4–5	Same as <i>d</i> -amphetamine (urinary pH-dependent) may have a greater central over peripheral effect ^c
Methylphenidate HCl ^b	10–60 mg (30–100 mg)	3–4	Same as amphetamines; better therapeutic index than <i>d</i> -amphetamine with less reduction of appetite or increase in blood pressure; short duration of action
Pemoline	20–115 mg (37.5–150 mg)	16–18	Less sympathomimetic effect; milder stimulant; slower onset of action; a tendency for drug build-up; occasionally produces liver toxicity; not a controlled substance
Mazindol ^d	2–6 mg (NA)	33–55	Weaker CNS stimulant effects; anorexia, dry mouth, irritability, headaches, gastrointestinal symptoms; reported to have less potential for abuse
Other Agents for treatment of EDS			
Modafinil	100–400 mg (NA)	8–14	No peripheral sympathomimetic action; headaches; nausea; reported to have less potential for abuse
Caffeine ^e	100–200 mg (NA)	3.5–5	Palpitations, hypertension; weak stimulant effect; 100 mg of caffeine roughly equivalent to one cup of coffee
MAO inhibitors with alerting effect			
Selegiline ^b	5–40 mg (NA)	0.15 ^f	Low abuse potential; partial (10–40%) interconversion to amphetamine
Brofaromine	150 mg (NA)	12–19	Reversible MAOA selective inhibitor

^aDosages recommended by the ASDA (90) are listed in parentheses (usual starting dose and maximal dose recommended).

^bDemonstrated anticataplectic effects in narcoleptic dogs.

^cMethamphetamine is reported to have more central effects (38) and may predispose more to amphetamine psychosis (139). The widespread misuse of methamphetamine had led to severe legal restriction on its manufacture, sale; and prescription in many countries (112). Note that the molecular weight of this compound is about half that of *d*- and *l*-amphetamine; thus, methamphetamine contains twice as much active molecules as *d*- or *l*-amphetamine per mg dose. *L*-amphetamine (dose range 20–60 mg) is not available in the US, but probably has no advantage over *d*-amphetamine in the treatment of narcolepsy (slightly weaker stimulant).

^dDemonstrated anticataplectic effects in humans.

^eCaffeine can be bought without prescription in the form of tablets (NoDoz, 100 mg; Vivarin 200 mg caffeine) and is used by many patients with narcolepsy prior to diagnosis.

^fHalf-lives of metabolites (amphetamine and methamphetamine) are long.

Of importance is the report that in animals, amphetamine-like stimulants are neurotoxic at high doses for catecholaminergic (e.g., dopaminergic) neurons (127).

The clinical use of stimulants in narcolepsy has been the subject of a recent American Sleep Disorders Association (ASDA, now American Academy of Sleep Medicine) Standards of Practice publication (9). Typically, the patient is started at a low dose, which is then increased progressively to obtain satisfactory results (Table 131.2). Studies have shown that daytime sleepiness can be greatly improved subjectively, but that sleep variables are never completely normalized by stimulant treatment (92). Low efficacy compounds/milder stimulants (e.g., modafinil, or more rarely, pemoline) are usually tried first. More effective amphetamine-like stimulants (i.e., methylphenidate, *d*-amphet-

amine, and methamphetamine) are then used if needed. The final dose of stimulant medication used varies widely from patient to patient, depending on tolerance, personality, efficacy, and lifestyle (from no stimulant treatment to very high doses). Patient input and work environment is very important. Some patients prefer to use high doses of long-acting, slow-release preparations to stay awake all day long, whereas others combine lower doses and short half-life derivatives (e.g., methylphenidate) with scheduled napping. Stimulant compounds are generally well tolerated. Minor side effects such as headaches, irritability, nervousness, tremors, anorexia, palpitations, sweating, and gastric discomfort are common (Table 131.2). Cardiovascular impact such as increased blood pressure is possible considering established sympathomimetic effects in animals, but has been

remarkably difficult to document in human studies (145). Surprisingly, tolerance rarely occurs in this patient population and “drug holidays” are not recommended by the American Academy of Sleep Medicine (90). Rather, a slight increase in dosage is preferable. Exceptionally, psychotic complications are observed, most often when the medications are used at high doses and chronically disrupt nocturnal sleep.

Amphetamine was first used to treat narcolepsy in 1935 (120), only 8 years after Alles initially synthesized it (5). Both the *l*- and *d*-isomers have been used for the treatment of narcolepsy, either in isolation or as a racemic mixture (available in the United States). The *d*-isomer is a slightly more potent stimulant (113,115) and is most generally used. *L*-Amphetamine is occasionally used in some European countries (dose range 20 to 60 mg) (112). *D*-Amphetamine is the second most frequently prescribed narcolepsy treatment after methylphenidate (8). It is well absorbed by the gastrointestinal tract and partially metabolized in the liver using aromatic and aliphatic hydroxylation. This process yields parahydroxyamphetamine and norephedrine, respectively, both of which are biologically active (158). Amphetamine is metabolized into benzoic acid (23%), which is subsequently converted to hippuric acid or parahydroxyamphetamine (2%). This in turn is converted to parahydroxynorephedrine (.4%). Thirty-three percent of the oral dose is excreted unchanged in the urine. Importantly, urinary excretion of amphetamine and many amphetamine-like stimulants is greatly influenced by urinary pH. Amphetamine is a weak base and at a physiologic pH, it exists mainly as a charged amine $[RNH_3]^+$, which is poorly reabsorbed in the renal tubules. Acidifying the urine thus favors the excretion of the charged form of the amine (16), increases urinary excretion versus liver catabolism, and reduces the half-life. At urinary pH 5.0, the elimination half-life of amphetamine is very short (about 3 to 5 hours) but at pH 7.3 it increases to 21 hours (16). Sodium bicarbonate delays excretion of amphetamine and prolong its clinical effects, whereas ammonium chloride shortens amphetamine toxicity. Finally, dextroamphetamine is available as a sulfate-base derivative or as spansule (slow-release) capsules.

Methamphetamine is the most efficacious and most potent amphetamine derivative available. This compound is extremely useful in subjects with severe sleepiness who need high doses. The addition of a methyl group makes this derivative more lipophilic, thus increasing CNS penetration and providing a better central over peripheral profile. The widespread misuse of methamphetamine has led to severe legal restriction on its manufacture, sale, and prescription in many countries (112), but it is available in the United States. It should also be noted that the molecular weight of the most commonly used form of methamphetamine (hydrochloride) is about half that of *d*- and *l*-amphetamine salt (sulfate). Methamphetamine preparations thus contain twice as many active amphetamine molecules when com-

pared to *d*- or *l*-amphetamine per mg dose. The simple chlorate to sulfate formulation difference largely explains the higher potency of methamphetamine.

Yoss and Daly introduced methylphenidate for the treatment of narcolepsy almost 50 years ago (160). It is now the most commonly prescribed stimulant medication in the United States, with 46% of narcoleptic patients using the compound on a regular basis (8). Part of its popularity is owing to its relatively short duration of action (approximately 3 to 4 hours). This property allows narcoleptic patients to use the compound on an as-needed basis while keeping open the possibility of napping. The compound is also reported to produce fewer psychotic complications at high doses (116). A slow release formulation is available but less frequently used.

Pemoline is generally better tolerated than methamphetamine or *d*-amphetamine but it is also less efficacious and less potent, and occasionally produces liver toxicity. After taking a therapeutic dose of pemoline (40 mg), peak levels in serum are reached within 4 to 6 hours. The half-life is 16 to 18 hours. Pemoline is partially metabolized by the liver. Metabolites include pemoline conjugates, pemoline dine, and mandelic acid. After oral administration of 40 mg of pemoline, 35% to 50% of the dose is excreted in the urine within 32 hours, and only a minor fraction is present as metabolites (41). The long duration of action of pemoline may be associated with a better compliance in narcoleptic patients (130). Pemoline most selectively blocks dopamine reuptake and only weakly stimulates dopamine release. Fatal hepatotoxicity has been reported and may be dose related (17,142). Pemoline should not be prescribed to patients with impaired hepatic function, and hepatic function should be carefully monitored during chronic drug administration. The recent introduction of modafinil, a novel wake-promoting agent with a similar profile and fewer side effects, has greatly diminished the use of this compound in narcolepsy.

Mazindol is less frequently used because of its weaker stimulant activity (58). It is a weak releasing agent for dopamine, but it also blocks dopamine and norepinephrine reuptake with high affinity (103). Mazindol is effective for both excessive daytime sleepiness and cataplexy (58). Mazindol is absorbed quantitatively at a medium rate from the gastrointestinal tract, and the peak blood concentration is reached after 2 to 4 hours. The half-life of clearance from blood was estimated at 33 to 55 hours (47).

Modafinil and Other Wake-Promoting Agents

Modafinil, a compound structurally distinct from amphetamines, has recently been approved in the United States for the treatment of narcolepsy and essential hypersomnia. This compound is also increasingly explored to treat other conditions, such as residual sleepiness in treated obstructive sleep

apnea or fatigue in multiple sclerosis. Modafinil has been available in France since 1986, and long-term follow-up suggests no remarkable side-effect profile and low abuse potential. Clinical trials in France and Canada have shown that 100 to 300 mg of modafinil is effective for improving daytime sleepiness in narcoleptic and hypersomnolent subjects without interfering with nocturnal sleep. It has limited efficacy on cataplexy and the symptoms of abnormal REM sleep (15,19,21). Recent double-blind trials on 283 narcoleptic subjects in 18 centers in the United States and on 75 narcoleptic subjects in 11 centers in Canada revealed that 200 and 400 mg of modafinil significantly reduced sleepiness and improved patients' overall clinical condition (1, 26). However, it is also reported that patients who have been previously treated with methylphenidate may respond more poorly to modafinil (26). Modafinil is well tolerated by these subjects, and adverse experiences with modafinil use occur at rates comparable to placebo (1,26). In humans, modafinil exhibits a linear pharmacokinetic profile for doses ranging from 50 to 400 mg, with a terminal elimination half-life ($t_{1/2}$) of 9 to 14 hours (159). Modafinil is extensively metabolized to two major pharmacologically inactive metabolites, modafinil acid and modafinil sulfone, which are renally excreted. Less than 10% of the oral dose of modafinil is excreted unchanged, and 40% to 60% is excreted as unconjugated acid in urine (159).

The exact mode of action of modafinil is still uncertain. The wake promoting effects of the compounds have been suggested to involve $\alpha 1$ -adrenergic stimulation (67) and/or serotonergic-GABAergic interactions (37). The compound interacts with the dopaminergic system at high doses and is neuroprotective in the MTPP model (37,39). Recent work by our group rather suggests that selective, but low-potency, dopamine reuptake inhibition mediates the wake-promoting effects of modafinil (84,103). In rats, modafinil acutely decreased both REM and non-REM sleep in rats for up to 5 to 6 hours without inducing a secondary rebound hypersomnolence (34). This contrasts with the intense recovery sleep seen after amphetamine administration (34). This unique feature of modafinil (wakefulness without rebound hypersomnia) may be explained by the pharmacokinetics profile of the compound (modafinil has a significantly longer half-life than amphetamine or methylphenidate) (159). Alternatively, this important difference may be owing to its unique pharmacodynamic profile, for example, dopamine uptake inhibition versus dopamine release effects for amphetamine (34).

Several factors make modafinil an attractive alternative to amphetamine-like stimulants. First, animal studies suggest that the compound does not affect blood pressure as much as amphetamines do (50) (potentially the result of its lack of effects on adrenergic release or reuptake). This suggests that modafinil might be useful for patients with a heart condition or high blood pressure. Second, animal data suggest no neurotoxic effects and no or less rebound hyper-

somnolence on withdrawal. Third, data obtained to date suggest that tolerance and dependence are limited with this compound (15), although a recent animal study reports a cocaine-like discriminative stimulus and reinforcing effects of modafinil in rats and monkeys, respectively (42). Finally, clinical studies suggest that the alerting effect of modafinil might be qualitatively different from that observed with amphetamine (15). In general, patients feel less irritable and/or agitated with modafinil than the amphetamines (15). In animal experiments, modafinil did not induce behavioral excitation, as measured by lack of locomotor activation (35). Considering the many advantages of modafinil over amphetamine treatment (fewer cardiovascular side effects, low abuse potential, lower levels of tolerance, and less rebound sleep), modafinil may replace amphetamine-like stimulants as a first-line treatment for excessive daytime sleepiness.

Caffeine, a xanthine derivative, may be the most popular and widely consumed stimulant in the world. The average cup of coffee contains about 50 to 150 mg of caffeine. Tea (25 to 90 mg/5 oz), cola drinks (35 to 55 mg/12 oz), chocolate (15 to 30 mg/1 oz), and cocoa (2 to 20 mg/5 oz) also contain significant amounts of caffeine. Taken orally, caffeine is rapidly absorbed, taking 47 minutes to reach maximum plasma concentration. The half-life of caffeine is about 3.5 to 5 hours (143). A slow-release soft gelatin caffeine capsule is also available with a mean delay to peak plasma concentration of 4 hours (143). The behavioral effects of caffeine include increased mental alertness, faster and clearer flow of thought, increased wakefulness, and restlessness (121). Fatigue is reduced, and the need for sleep is delayed (121). Physical effects of caffeine include palpitations, hypertension, and increased secretion of gastric acid and increased urine output (121). Heavy consumption (12 or more cups a day, or 1.5 g of caffeine) can cause agitation, anxiety, tremors, rapid breathing, and insomnia (121). The mechanism of action of caffeine involves antagonism of an adenosine (nonspecific) receptor and of adenosine-induced neuronal inhibition (121). Considering the fact that 100 mg of caffeine is roughly equivalent to one cup of coffee, caffeine does not possess the efficacy to counteract the pathologic sleepiness seen in narcolepsy. Nevertheless, caffeine in the form of tablets can be bought without a prescription (NoDoz, 100 mg caffeine; Vivarin, 200 mg caffeine), and is used by many patients with narcolepsy prior to diagnosis.

Antidepressants and the Pharmacologic Treatment of Cataplexy

Amphetamine stimulants have little effect on cataplexy, and additional compounds are most often needed to control cataplexy if the symptom is severe enough to warrant treatment. Since the 1960s, it has been known that imipramine is very effective in reducing cataplexy (2). Together with protriptyline and clomipramine, these tricyclic antidepres-

TABLE 131.3. ANTIDEPRESSANTS CURRENTLY USED AS ANTICATAPLEPTIC AGENTS

Antidepressant Compounds	Usual Daily Doses	Side Effects/Note
Commonly used compounds		
Imipramine	10–100 mg	Dry mouth, anorexia, sweating, constipation, drowsiness (51).
Desipramine	25–200 mg	Effects and side effects similar to those of imipramine demethylated metabolite of imipramine (51).
Protryptiline	5–60 mg	Some reports suggest improvement in vigilance measures (49), whereas other reports are negative (no improvement in performance or daytime sleepiness) (93).
Clomipramine	10–150 mg	Digestive problem, dry mouth, sweating, tiredness, impotence (45,140). Its active metabolite, desmethylclomipramine, is shown to be more potent in the canine model (97).
Fluoxetine ^a	20–60 mg	Nausea, dry mouth, fewer side effects, long half-life (60 hours); no anticholinergic or antihistaminergic effects; good anticataplectic effect but less potent than clomipramine (63).
Some clinical trials, but less commonly used		
Zimelidine ^a	100 mg	Less sedative effect; no anticholinergic or antihistaminergic effects; potent anticataplectic compound (94). Its active metabolite, norzimelidine, is shown to be more potent than zimelidine in the canine model (97).
Femoxetine ^a	600 mg	Fewer side effects than clomipramine but less potent (136) pharmacologic effects similar to fluoxetine.
Fluvoxamine ^a	50–300 mg	Gastrointestinal side effects (134). No active metabolites; pharmacologic profile similar to fluoxetine; less active than clomipramine.
Paroxetine ^a	20–60 mg	Less anticholinergic effects; cardiovascular side effects; effective on cataplexy (with yohimbine) (119).
Viloxazine	100–300 mg	Few side effects; selective but low potency adrenergic uptake inhibitor, active on human cataplexy and possibly sleepiness, but not available in most countries (40,43); effective anticataplectic agent in canines (85).
Venlafaxine	150–375 mg	New serotonergic and adrenergic uptake blocker; no anticholinergic effects, effective on cataplexy sleepiness in a small pilot study (146), low potency.

^aClinical trial results using these compounds (63,94,134,136) suggest that SSRIs are effective for the treatment of cataplexy or REM sleep related symptoms while inducing fewer side effects than classical tricyclic antidepressants. It is, however, still not conclusive whether SSRIs can be recommended as a first line of treatment, because SSRIs are usually less potent than tricyclic antidepressants (136). SSRIs, selective serotonin reuptake inhibitors.

sants are now the most commonly used anticataplectic agents (8) (Table 131.3). Other antidepressant compounds of the tricyclic family have also been used with some success (Table 131.3). The use of tricyclic antidepressants in the treatment of cataplexy, however, is hampered by a number of problems. The first is the relatively poor side-effect profile of most tricyclic compounds. These are mostly owing to their anticholinergic properties, leading to dry mouth (and associated dental problems), tachycardia, urinary retention, constipation, and blurred vision (Table 131.3). Additional side effects are weight gain, sexual dysfunction (impotence and/or delayed orgasm), tremors, antihistaminergic effects leading to sedation and occasionally orthostatic hypotension owing to the α 1-adrenergic blockade effects of some compounds. In this respect, protryptiline is often preferred because of its previously reported mild stimulant effect (49). Nighttime sleep might also become more disturbed because of increased muscle tone and leg movements (122,152).

The cardinal pharmacologic property of tricyclic antidepressants is their ability to inhibit the reuptake of norepinephrine (and epinephrine) and serotonin (14). The degree of uptake inhibition of norepinephrine and serotonin is quite variable depending on the compound and the existence of active metabolites (mostly active on adrenergic uptake) (14). Additionally, some tricyclic compounds, such as protryptiline, are also weak dopamine reuptake inhibitors (14).

The introduction of newer antidepressants with selective serotonergic uptake inhibition properties (e.g., SSRIs) and no anticholinergic effects, such as fluoxetine, fluvoxamine, paroxetine, sertraline, femoxetine, zimelidine, and trazodone has raised hope that the control of cataplexy could be achieved with fewer side effects. In general, however, clinicians have been less impressed with the potency of the serotonergic compounds on cataplexy (63,94,136). This experience parallels experiments in canine narcolepsy suggesting that adrenergic, not serotonergic, uptake inhibition me-

diates the anticataplectic effects of most antidepressant medications (85,97). Among the SSRIs, fluoxetine is a viable alternative to tricyclic compounds (63). Fluoxetine has a good side-effect profile and may induce less weight gain, a significant advantage for some patients. Venlafaxine, a novel serotonergic and adrenergic reuptake blocker, also has been used recently with good success. Finally, the introduction of reboxetine, a specific adrenergic reuptake blocker, may offer a novel and more effective alternative to SSRIs and tricyclic antidepressants based on animal data.

In addition to the antidepressants listed in Table 131.3, γ -hydroxybutyrate (GHB), a hypnotic compound discussed in more detail in the section on disrupted nocturnal sleep, has been shown to alleviate cataplexy during long-term administration. GHB is an endogenous constituent of mammalian brains, synthesized locally from GABA, which may play a role as an inhibitory neuromodulator (18). Monoamine oxidase inhibitors (MAOIs) are known to potentially reduce REM sleep, and are therefore excellent candidate anticataplectic agents; however, these compounds are less often used owing to their poor safety profile. Selective or reversible MAOIs have recently become available, but clinical trials of these compounds at a large scale are still not available (104).

Treatment of Sleep Paralysis and Hypnagogic Hallucinations

The treatment of these two symptoms is not well codified. Hypnagogic hallucinations can be quite bothersome, and often occur in patients who also suffer from frequent nightmares. As they are a manifestation of sleep onset REM sleep, the compounds that suppress REM sleep are usually helpful in alleviating this symptom, and tricyclic antidepressant treatment has been reported to have some beneficial effects (149). Sleep paralysis only rarely requires treatment, but tricyclic antidepressants are also very effective for preventing this symptom. Recently, high doses (60 mg QD) of fluoxetine have been advocated as a very active treatment for isolated sleep paralysis (61). GHB is also effective in suppressing hypnagogic hallucinations, sleep paralysis, and cataplexy (72).

GHB and Treatment of Disturbed Nocturnal Sleep

Insomnia is a major complaint in narcoleptic subjects. Several studies reported that benzodiazepine hypnotics are effective in consolidating nighttime sleep in patients with narcolepsy (151). GHB, a compound with remarkable REM- and SWS-inducing properties, has also been used for consolidating nighttime sleep, an effect that leads to decreased sleepiness and cataplexy the following day (24, 25,137,138). Large-scale double-blind placebo controlled clinical trials are in progress in the United States to re-

establish GHB as a first line treatment for narcolepsy-cataplexy (104). The compound is especially useful in patients with severe insomnia and cataplexy who do not tolerate well the side effects of antidepressant medication on sexual potency. The mode of action of GHB on sleep and sleep-related symptoms is unknown, but may involve decreased dopaminergic tone after GHB (18). Because of its positive effects on mood and libido, its SWS-enhancing properties, and a subsequent increase in growth hormone release, the drug is widely abused by athletes and other populations (31, 70); therefore, several states have passed legislation restricting access to GHB requesting by prescriptions for its use. The compound has also been reported to increase periodic leg movements in narcoleptic patients (27).

GHB is absorbed 15 to 20 minutes after oral ingestion, and peak plasma concentration occurs at 60 to 120 minutes. The elimination half-life is 20 minutes (111,157). Exogenous GHB is almost completely eliminated by oxidative biotransformation to carbon dioxide and water, less than 5% is detected unmetabolized in the urine (111,157). At low doses, GHB is anxiolytic and myorelaxant. At intermediate doses, GHB increases slow wave sleep and REM sleep (64). However, because of the short half-life of the compound, its effects on sleep architecture are short-lasting (about 3 to 4 hours) and administration thus has to be repeated two to three times during the night (20 to 40 mg/kg per night). Overdoses (a single dose of 60 to 100 mg/kg) induce dizziness, nausea, vomiting, confusion, agitation, epileptic seizures, hallucinations, and coma with bradycardia and respiratory depression (66). Death has been reported and the therapeutic window is narrow ($LD_{50} = 5$ - to 15 -fold the dose inducing coma). Although the compound is structurally related to GABA and is a natural metabolite of the neurotransmitter, its mode of action involves specific non-GABAergic binding sites (75). GHB and GABAB receptors may interplay functionally (71). GHB is also known to inhibit firing of dopaminergic neurons, dopamine release, and dopamine synthesis (156).

PHARMACOLOGY AND NEUROCHEMISTRY OF CANINE NARCOLEPSY

Pharmacologic Control of Canine Cataplexy

The canine model of the disorder has been used to pharmacologically dissect the mechanisms involved in the control of cataplexy and alertness. These experiments led us to conclude that the control of cataplexy and REM sleep are very similar, although in several aspects, cataplexy is not identical to natural REM sleep muscle atonia (102). Activation of cholinergic systems using the acetylcholinesterase inhibitor physostigmine, for example, greatly exacerbates cataplexy (12,33). This cholinergic effect is mediated via muscarinic receptors because muscarinic stimulation aggravates cata-

plexity, whereas its blockade suppresses it, and nicotinic stimulation or blockade has no effect (12,33). These results parallel data obtained on cholinergic systems and REM sleep control. (See refs. 144 and 148 for review.)

Monoaminergic transmission is also critical for the control of cataplexy. All therapeutic agents currently used to treat cataplexy (i.e., antidepressants or MAOIs) are known to act on these systems. Furthermore, whereas cholinergic neurons are activated during REM sleep, the firing rate of monoaminergic neurons in the brainstem, such as in the locus ceruleus (LC) and raphe magnus, are well known to be dramatically depressed during this sleep stage (10,153). In contrast, dopamine neurons of the ventral tegmental area (VTA) and substantia nigra (SN) do not significantly change their activity during the sleep cycle (89,154).

Although antidepressants and MAOIs enhance monoaminergic transmission, these compounds generally lack specificity and globally enhance serotonergic, adrenergic, and dopaminergic transmission. Using newer uptake inhibitors and releasing agents with selective monoamine effects, we have demonstrated that the presynaptic activation of adrenergic, but not dopaminergic or serotonergic, systems mediates the anticataplectic effects of currently available antidepressive treatments (85,97). This suggests that cataplexy, and possibly REM sleep atonia are more selectively modulated by adrenergic systems. Interestingly, presynaptic activation of dopamine transmission with dopamine uptake inhibitors had potent alerting effects (103) but no effect on cataplexy (85).

Receptor-Specific Regulation of Cataplexy: A Pathologic Model of REM Sleep Atonia

More than 200 compounds with various pharmacologic properties (cholinergic, adrenergic, dopaminergic, serotonergic, prostaglandins, opioids, benzodiazepines, GABAergic, and adenosinergic) have been studied in the narcoleptic canine model. (See ref. 104 for a recent review.) Although many compounds, such as M2 antagonists, α 1-agonists, α 2-antagonists, dopamine D2(3) antagonists, 5-HT1a agonists, TRH analogues, prostaglandin E2, and L type Ca^{2+} channel blockers reduce cataplexy, very few compounds significantly aggravate cataplexy. Because REM sleep can be easily disturbed nonspecifically in pharmacologic studies, aggravations in cataplexy are considered to be the most specific effect. The stimulation of muscarinic M2 (non-M1) receptors significantly aggravates cataplexy. Among monoaminergic receptors, the postsynaptic adrenergic α 1b receptors (79,99) and presynaptic α 2 receptors (100) were also found to aggravate cataplexy, a result consistent with a primary adrenergic control of cataplexy. It was also found that dopamine D2(3) agonists significantly aggravated cataplexy and induced drowsiness in these animals. To date, no other receptor ligands (e.g., adenosinergic, his-

taminergic or GABAergic) have been found to aggravate cataplexy (104).

The cataplexy-inducing effects of D2(3) compounds on cataplexy, however, are difficult to reconcile with the fact that dopaminergic uptake blockers and releasing agents have absolutely no effect on cataplexy (85). Interestingly, the aggravation of cataplexy by D2(3) agonists is blocked by adrenergic, but not dopaminergic, uptake inhibitors (105), suggesting some functional interaction between the dopaminergic and adrenergic systems for the regulation of cataplexy.

Presynaptic Stimulation of Dopamine Transmission Mediates the EEG Arousal Effects of Amphetamine-like Stimulants

Amphetamine-like CNS stimulants currently used clinically for the management of sleepiness in narcolepsy presynaptically enhance monoaminergic transmission; however, these compounds also lack pharmacologic specificity. In order to study the mode of action of these compounds on daytime sleepiness, the stimulant properties of several dopaminergic and adrenergic uptake inhibitors were quantified and compared to the effects of amphetamine and modafinil using 6-hour daytime polygraphic recordings in the canine narcolepsy model (103). In spite of their lack of effects on cataplexy, all dopaminergic uptake inhibitors induced significant EEG arousal. In contrast, nisoxetine and desipramine, two potent adrenergic uptake inhibitors, had little effect on EEG arousal but significantly suppressed REM sleep, a finding that is consistent with their potent anticataplectic effects. Furthermore, the *in vivo* potency of dopamine uptake inhibitors on EEG arousal correlates well with the *in vitro* dopamine transporter (DAT), but not with the norepinephrine transporter (NET), binding affinities for individual compounds (103). These results are consistent with the hypothesis that presynaptic modulation of dopamine mediates the EEG arousal effects of these compounds. Interestingly, it was also found that modafinil binds to the DAT site with low affinity (84,103), similar to the affinity range for amineptine (a dopamine uptake inhibitor that also enhances EEG arousal in our model). Thus, DAT binding may also contribute to the stimulant properties of modafinil.

Midbrain Dopaminergic Systems Are Involved in the Regulation of Cataplexy and Excessive Daytime Sleepiness in Narcolepsy

The site of action for dopaminergic modulation of cataplexy recently has been identified using microdialysis experiments. D2(3) agonist injections into the ventral tegmental area (VTA) (126) and substantia nigra (SN) (53), two re-

gions where dopaminergic cell body autoreceptors are densely packed, was found to reproduce the effects of small intravenous doses of dopamine agonists or antagonists on cataplexy (98). An injection of the same compounds in the pontine reticular formation (PRF), where dopamine autoreceptors are less densely packed, has no effect (126). This suggests that the D2(3) effect is genuinely mediated by autoreceptor stimulation and that cataplexy may be modulated by changes in dopaminergic activity originating from the VTA and SN. The perfusion of dopamine uptake inhibitors in these midbrain dopaminergic nuclei does not modify cataplexy (53). Because various electrophysiologic and pharmacologic studies have demonstrated that dopamine reuptake is of physiologic importance in the limbic forebrain, striatum, and cortical hemispheres, but not in midbrain dopaminergic neurons (108), acting sites for the dopaminergic regulation of cataplexy and sleepiness may be anatomically different. This may explain why D2(3) agonists induce both cataplexy and sleepiness (53,126), whereas dopamine uptake inhibitors only induce significant EEG arousal but have no effect on cataplexy (105). In this model, enhancement of DA transmission at the terminal region may be sufficient to induce a wake-promoting effect; however, reduction in the activity of DA neurons and interactions with adrenergic systems may be required for the modulation of cataplexy (101,105).

Cholinergic Hypersensitivity and the Regulation of Cataplexy

The effects of cholinergic stimulation in various brain areas were also examined in narcoleptic and control canines. Local injection or perfusion of carbachol, a predominantly muscarinic agonist, into the PRF was found to aggravate canine cataplexy in a dose-dependent fashion (125). Acetylcholine release in the PRF was significantly elevated during the FECT when narcoleptic animals had multiple cataplectic attacks, while no increase in acetylcholine levels was observed in control animals (124). The results obtained in the PRF with cholinergic agonists and acetylcholine release were expected considering the well-established role of pontine cholinergic systems in the regulation of REM sleep. In this experiment, however, narcoleptic dogs were found to be consistently more sensitive to cholinergic stimulation than control animals (125). More surprisingly, however, it was also found that the local injection of carbachol unilaterally or bilaterally (2 to 10 nmol per site) into the BF (rostral to the preoptic area, in the vertical or horizontal limbs of the diagonal band of Broca and medial septum) also dose-dependently aggravated cataplexy (107). This manipulation induced long-lasting muscle atonia episodes with desynchronized EEG in narcoleptic canines (107). The same pharmacologic manipulation (10 nmol of carbachol) did not induce cataplexy in normal animals, but rather induced wakefulness, as previously reported in rats and cats (11).

The BF is anatomically connected with the limbic system, which is regarded as a critical circuit for integrating emotions. Furthermore, BF neurons are known to respond to the arousing property of appetitive stimuli (131), which potently induce cataplexy in narcoleptic dogs. Considering the fact that emotional excitation is an alerting stimulus in normal animals, but induces cataplexy in narcoleptic animals, the BF may be involved in triggering a paradoxical reaction to emotions—*atonia* rather than *wakefulness*—in narcoleptic animals.

Monoaminergic/Cholinergic Imbalance and Hypocretin Deficiency

As detailed, cholinergic and monoaminergic imbalances are central to the pathophysiology of narcolepsy and the control of natural REM sleep. The fact that impaired hypocretin transmission is involved in both animal and human narcolepsy indicates that the hypocretin peptides must be tightly connected functionally with monoaminergic and cholinergic systems. Deficit in the production of the hypocretin ligand, as well as mutations in one of the receptors (Hcrtr 2), induces narcolepsy in mice and dogs, respectively (30, 68). In humans, abnormalities in the production of the ligands are most likely to be the etiology of the disease in most cases (106).

De Lecea and associates first identified hypocretins using a subtraction technique aimed at the isolation of hypothalamic-specific transcripts (32). The same neuropeptide system was independently identified by Sakurai and associates and was named *Orexin* (133). These authors isolated two new neuropeptides, *Orexin A* and *B*, as endogenous ligands for previously poorly characterized orphan G-protein-coupled receptors (GPCRs). The hypocretin receptors are closely related to other neuropeptide GPCRs, such as the Y_2 neuropeptide Y receptor (26% identity) and the TRH receptor (25%). Hypocretin-1 and -2 correspond to *Orexin A* and *B*, respectively (132). These molecules are processed from the same precursor peptide (preprohypocretin). Hypocretins bind and activate two closely related GPCRs, the Hcrtr 1 (Ox1R) and Hcrtr 2 (Ox2R) receptors (133). Hcrtr 1 is selective for hypocretin-1 (20 to 100 \times higher affinity) whereas Hcrtr 2 exhibits similar affinity for both hypocretin-1 and -2 (133). Preprohypocretin mRNA and hypocretin-1 or -2 immunoreactivity colocalize in a small group of neurons located within and around the lateral hypothalamic area (LHA) in adult rat brains (32,118,133).

Hypocretins were initially believed to control appetite and food intake (thus the name *Orexin*, appetite in Greek) because of their discrete localization within the lateral hypothalamus. Similar to neuropeptide Y and leptin, hypocretins play a role in metabolic and endocrine regulation and have effects on food intake (95,133). The finding that hypocretin-containing neurons diffusely innervate numerous brain regions in addition to the hypothalamus (cerebral cortex,

limbic system, brainstem, and the spinal cord) (118), however, suggested that hypocretins might have other functions. Regulatory effects on blood pressure, body temperature, and the sleep-wake cycle were suggested (118). Hypocretin neurons in the LHA project to brain regions responsible for the regulation of vigilance (e.g., LC, VTA and the tuberomammillary histaminergic nucleus) and REM sleep (LC, dorsal raphe, and pontine cholinergic nuclei and PRF) (118). These anatomic and physiologic findings, taken together with the fact that deficits in hypocretin neurotransmission induce the narcolepsy phenotype, suggest that that hypocretins are the major neuromodulators for monoaminergic and cholinergic systems and hypocretins modulate sleep and sleep-related phenomena by interaction with these classical neurotransmitters.

PERSPECTIVES AND FUTURE DIRECTIONS

The discovery that a deficit in hypocretin neurotransmission, as revealed by the CSF hypocretin studies (106), frequently causes human narcolepsy opens the door to new diagnostic and therapeutic strategies. Measuring hypocretin levels in the CSF or other biological fluids may soon be used as a diagnostic test for narcolepsy. Early diagnosis may be critical for a disorder with peripubertal onset and a dramatic psychosocial impact. New therapeutic strategies should also be developed. All compounds currently used for the treatment of narcolepsy act symptomatically by enhancing monoaminergic transmission, likely downstream of the hypocretin neurotransmitter system (see section for monoaminergic/cholinergic imbalance and hypocretin deficiency). If reduced neurotransmission of hypocretin is a primary deficit in human narcolepsy and hypocretin receptors are still functional, supplementing transmission with hypocretins (and analogues) may have significant therapeutic effects in human narcolepsy (both on EDS and cataplexy).

Hypocretins are also likely to join acetylcholine and monoamines as critical sleep neurotransmitters. Basic research work relevant to the issue of sleep control will proceed at a rapid pace. Which hypocretin projections are most important for sleep control? How is the hypocretin system regulated across the sleep cycle? The preferential localization of Hcrtr2 on tuberomammillary and SN/VTA neurons suggests a preferential role for histaminergic and dopaminergic systems, but functional studies are lacking. Hypocretins are strongly excitatory in most cells studied, including monoaminergic cells (48,155). Removing an excitatory signal on these target cells could contribute to a monoaminergic hypoactivity. Similarly, the dense neuroanatomic distribution of Hcrtr2 in limbic structures such as the amygdala and the nucleus accumbens may explain cataplexy, a symptom triggered by emotions. Recent neuroimaging studies have shown that these regions are activated during natural REM sleep (74).

More work in the area of narcolepsy pathophysiology is also needed. Mutation screening studies of hypocretin genes indicate in narcolepsy-cataplexy very rare hypocretin system gene disease causing mutations, even in familial and non-HLA-DQB1*0602 positive narcoleptic subjects (36). This indicates some degree of disease heterogeneity and the possibility that other neuronal systems closely related to the hypocretin/narcolepsy system still remain to be discovered. Does the observation that most cases of narcolepsy have undetectable CSF hypocretin levels indicate that hypocretin cells are destroyed in human narcoleptic brains? The finding that narcolepsy is tightly associated with HLA suggests a possible autoimmune process directed against these LHA cells. Autoantibodies against hypocretins or a substance closely related to the hypocretin system/LHA may secondarily cause narcolepsy. The relationship between feeding regulation, energy metabolism, and narcolepsy also should be explored. The role of the hypocretin system in the pathophysiology of narcolepsy without cataplexy remains to be investigated. Taking into account a recent, rapid gain in narcolepsy research, further progress in identifying the cause of human narcolepsy is likely to proceed at a rapid pace.

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