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Although people with the movies, narcolepsy

After hearing the punch line of the joke, the teenager falls to the floor, almost as if actually punched. She remains there, completely unable to move. She hears her parents reassure her friends that they need not worry about her because she will be all right in a few minutes. She is embarrassed and frustrated as the episode continues, and her friends begin to leave. They bid her goodbye, but she is unable to respond. Although she cannot talk or move, she is otherwise in a state of high alertness, feeling, hearing and remembering everything that is going on around her. The episode lasts for five minutes, longer than her typical catalexies—which often last only seconds—but shorter than her longest episode, which lasted 25 minutes. Then it ends, almost as abruptly as it began. She gets up from the floor, and her everyday life resumes.

DOG AND MAN with narcolepsy experience an attack of **cataplexy**—the complete loss of muscle tone while awake and conscious—in a similar fashion. In both, the attack causes the head to droop and the back and legs to sag; it can progress to a complete loss of muscle tone. Cataplexy is distinct from the sleep attacks that afflict most narcoleptics: people hear and remember what is said around them, and dogs can track a moving object with their eyes.

COLEPSY

the disorder do not fall face-first into their soup as in is still a mysterious disease. But science has new leads

by Jerome M. Siegel

Cataplexy, the loss of skeletal muscle tone without loss of consciousness, is one of the defining symptoms of a puzzling neurological disorder called narcolepsy. The cataplectic attacks of narcolepsy are frequently prompted by laughter; other times, embarrassment, social interactions with strangers, sudden anger, athletic exertion or sexual intercourse may trigger an episode.

Another characteristic symptom of narcolepsy—and usually the most incapacitating one—is persistent daytime sleepiness. If you have ever gone without sleep for 48 hours, you have experienced the sleepiness that a narcoleptic lives with every day. In spite of being so sleepy, they tend to sleep poorly at night. And although they feel refreshed after a short nap, the sleepiness soon returns. As a result, narcoleptics fall asleep at dangerous or inappropriate times, as illustrated by the cartoon on the next page. Untreated, they are therefore at high risk for motor vehicle accidents and often have trouble reaching their potential in school and the workplace.

Within the past several years, researchers have begun to unravel the mysteries of this debilitating—but surprisingly common—disease. My colleagues and I have identified the specific regions of the brain that appear to be affected in cataplexy and have discovered that they are the same regions that normally prevent us from moving in synchrony with our dreams (for example, thrashing our legs when we dream we are in a race). We have also found the first evidence of neuronal degenera-

tion in narcolepsy. Other scientists have isolated a gene that when mutated can cause narcolepsy in dogs. Perhaps most intriguingly, there are hints that narcolepsy might be an autoimmune disease, in which the immune system attacks normal brain tissue as foreign.

This disorder has a number of extraordinary features. Besides cataplexy and sleepiness, two other classic symptoms are sleep paralysis and so-called hypnagogic hallucinations. Sleep paralysis is an inability to move when falling asleep or awakening. Although normal individuals may have short periods of sleep paralysis a few times in their lives, it is a daily occurrence for many narcoleptics. Hypnagogic hallucinations are dreamlike experiences during waking that often incorporate elements of the environment. They usually occur when narcoleptics are most sleepy. Not every patient suffers in exactly the same way, however. For instance, the severity of cataplexy and sleepiness varies among individuals.

Narcolepsy is also surprising in its wide range of incidence. It affects between one in 1,000 and one in 2,000 people in the U.S. Rates in other countries range from one in 600 in Japan to one in 500,000 in Israel. Genetic factors linked to ethnicity or possibly environmental conditions may be responsible for this variation. The overall incidence of narcolepsy in the U.S. is about 10 times that of amyotrophic lateral sclerosis (Lou Gehrig's disease), half that of multiple sclerosis, five times that of cystic fibrosis and about one quarter

that of Parkinson's disease. The first signs of narcolepsy typically begin in the teens or 20s. Symptoms worsen for a few years and then plateau.

Sleep and Narcolepsy

arcolepsy is linked to a disruption of the sleep control mechanism. The sleep cycle normally consists of two primary phases: so-called rapid eye movement (REM) sleep and non-REM sleep.

Non-REM sleep is a quiet sleep state. The muscles are relaxed but maintain some tone, breathing is regular, the cerebral cortex generates high-voltage waves, and consumption of energy by the brain is minimal. Although REM sleep shares the loss of consciousness of the environment seen in non-REM sleep, it is physiologically quite different. Breathing and heart rate are irregular; characteristic rapid eye movements occur; the cortex generates fast, irregular, low-voltage waves similar to those present in alert waking; vivid dreams take place; and brain metabolism often exceeds levels seen when the subject is awake. Tone in the postural muscles, such as those in the back and legs, is absent during REM sleep, although twitches occasionally break through the motor quiescence.

People who are not narcoleptic begin their nighttime rest with non-REM sleep, with REM sleep following roughly 90 minutes later. But narcoleptics frequently go straight into REM sleep. Because of this trait—and because nar-

WHAT IS NARCOLEPSY?



THIS ISN'T....

THIS IS!

narcoleptics experience loss of muscle tone and dreamlike hallucinations that normally occur only during REM sleep—researchers have hypothesized that these symptoms of narcolepsy result from the inappropriate triggering of some aspects of REM sleep.

Although sleep problems are the most common symptoms of narcolepsy, much of the basic research on the disease has used cataplexy as a starting point. Sleepiness is a normal phenomenon; it is the amount of sleepiness that is abnormal in narcolepsy. Therefore, it is difficult to know if particular episodes of sleepiness seen in narcoleptics are abnormal. Cataplexy, however, never occurs in normal individuals. It is easily quantified and has an abrupt onset that allows scientists to determine the time course of the neural events that trigger it. By observing and manipulating cataplexy, we hope to gain a clear insight into the pathology of narcolepsy.

Narcoleptic Dogs

A major advance in narcolepsy research occurred in the early 1970s, when investigators observed that some dogs display symptoms very similar to those of human narcoleptics. William C. Dement of Stanford University was given a litter of Doberman pinschers (and later a litter of Labrador retrievers), all of which were narcoleptic. The disease was transmitted as a recessive trait, which means that a particular dog developed the disease only if it inherited the trait from both its mother and its father. Accordingly, when Dement bred two narcoleptic dogs, all the offspring

were narcoleptic. The dogs experienced cataplexy during vigorous play or when they were excited by being offered their favorite foods.

My colleagues and I have conducted electrophysiological studies on such dogs to try to elucidate the causes of the strange symptoms of narcolepsy. We use tiny electrodes to record the electrical impulses from nerve cells, or neurons, in the brain stem as they communicate with cells in other areas of the brain and spinal cord.

We began our studies with recordings from the brain stem because of experiments conducted in the 1940s by Horace W. Magoun of Northwestern University. Magoun discovered that when he electrically stimulated the medial medulla (a part of the brain stem), muscle tone vanished, almost as if he had thrown a switch for preventing movement. At the time of this discovery, the polio epidemic was sweeping the U.S. Magoun hypothesized that damage to the medulla could be responsible for some of the increases in muscle tone seen in the acute phase of polio and could also be responsible for increased tone seen in other neurological diseases.

Magoun did not connect his observation to sleep, because his finding was made before the 1953 discovery of REM sleep and the subsequent discovery of its associated muscle paralysis. Studies in animals now suggest that although the main function of the muscle-tone control system in the medulla is in suppressing muscle activity in REM sleep, it also has a role in regulating the general level of muscle tone in waking. This region is inactive when animals are moving, moder-

ately active when animals sit or lie down, further activated during non-REM sleep and maximally active in REM sleep. When you try to relax or "turn off" your muscles, you are actually trying to "turn on" this brain region.

Based on Magoun's findings, we wondered whether unusual activity in the medial medulla might be responsible for the cataplectic episodes experienced by narcoleptics. In 1991 we found that this was indeed the case: neurons in this region fired when narcoleptic dogs had a cataplectic attack. What is more, we observed that in normal animals, cells in this part of the medial medulla fired at high rates only when the animals were in REM sleep. Our discovery made sense because we knew from other studies that REM sleep is the only time when normal individuals lose all muscle tone.

Extending this line of research, Elizabeth Schenkel in my laboratory demonstrated that otherwise normal animals whose medial medullas were damaged moved around during REM sleep, instead of being completely relaxed. Other studies by Michel Jouvet of Claude Bernard University in Lyon, France, and Adrian R. Morrison of the University of Pennsylvania had shown that damage to higher levels of the brain stem that connect with the medulla produced animals that raised their heads, walked and appeared to attack imaginary adversaries during REM sleep. For some reason, in narcolepsy a group of neurons that is supposed to be active only during REM sleep to suppress muscle tone and protect us from the elaborate motor programs that accompany our dreams is being triggered during waking [*see box on opposite page*].

Another series of studies carried out in my laboratory by Frank Wu indicates that a second group of nerve cells in an area of the brain stem called the locus coeruleus also plays a role in REM sleep and narcolepsy. These cells release norepinephrine, a molecule called a neurotransmitter that neurons use to communicate with one another. When norepinephrine is secreted into the bloodstream, it participates in the body's "fight-or-flight" response during emergencies. Norepinephrine-producing neurons in the locus coeruleus have been shown in normal animals to be active throughout waking but to be inactive when the animals are in REM sleep. Our experiments in narcoleptic dogs indicate that cells in the locus coeruleus become completely inactive

before and during cataplexy, just as they do during REM sleep.

The cessation of activity in norepinephrine-containing cells removes a source of excitation from motor neurons just as the parallel system in the medulla responsible for inhibiting motor neurons becomes active. The loss of excitation and concurrent increase of inhibition together are responsible for greatly reducing the activity and excitability of motor neurons

during charging, the muscles that they control relax. In REM sleep the reduction of motor neuron excitability prevents them from responding to the motor signals that accompany dreams. In cataplexy the same reduction in excitability prevents the motor neurons from responding to a narcoleptic's attempts to move.

Recording the activity of neurons in narcoleptic dogs has given us an insight into how cataplexy is triggered. But why do these inhibitory events occur

during waking in narcoleptics? Why are they not confined to REM sleep, as in healthy individuals?

There are no clear answers to these questions, but two genetic studies have recently yielded clues that might help solve the mystery. Emmanuel Mignot of Stanford and his co-workers have identified the gene responsible for narcolepsy in dogs. His research group has determined that the dogs carry a mutation in the receptor for a neurotransmitter

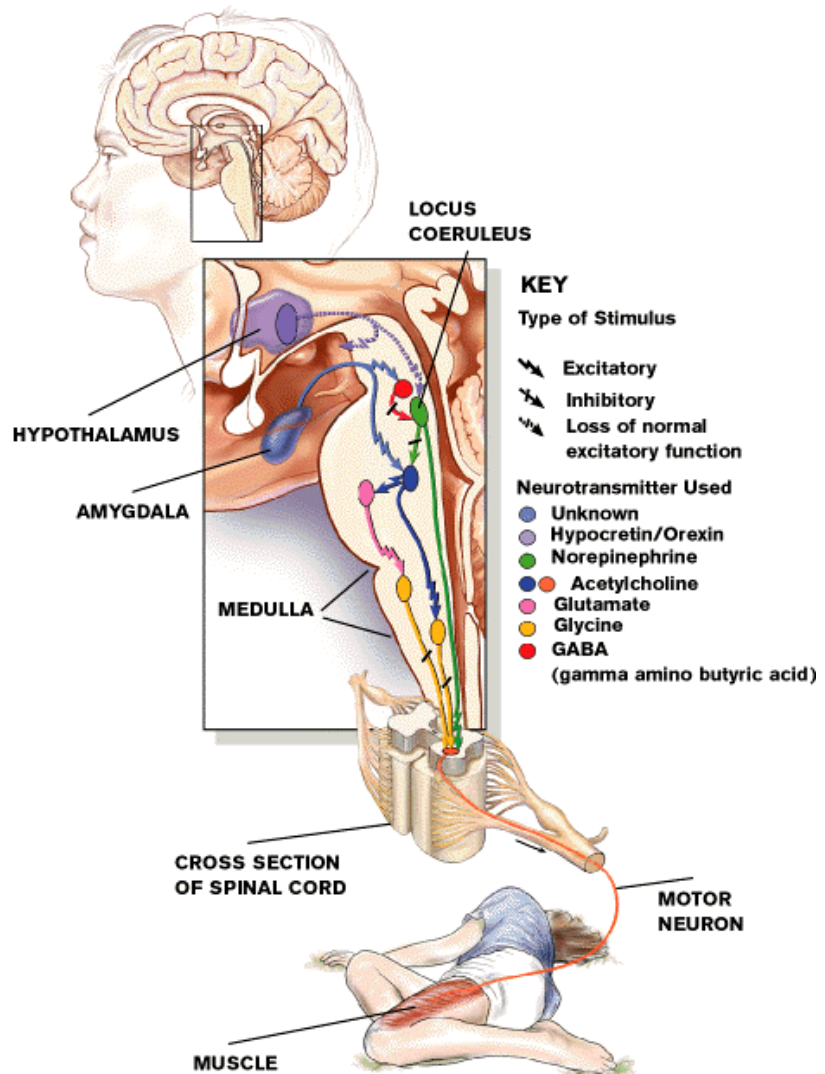
The Neural Circuitry of Narcolepsy

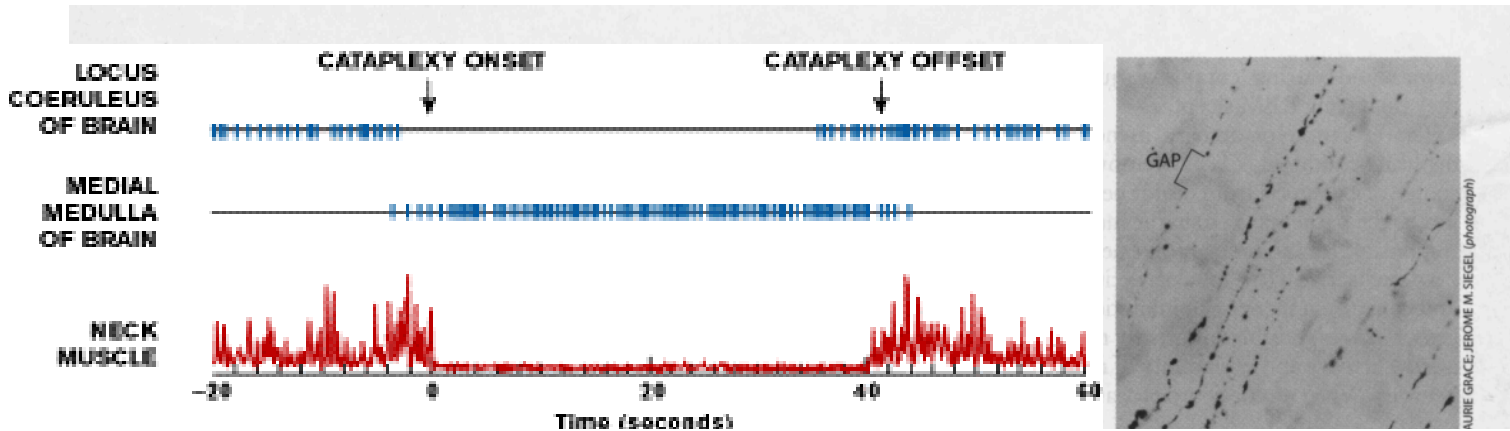
rain and spinal cord circuits that normally inhibit movement during sleep are triggered inappropriately during cataplexy attacks in narcolepsy, causing a loss of tone in the muscles that maintain posture. The figure illustrates one simplified model of how this might occur.

The degeneration of cells in the forebrain eliminates inhibitory signals that are important for regulating the activity of cells in the amygdala, a structure involved in emotional responses. The loss of the inhibitory signals in the amygdala causes increased activity in amygdala connections (light blue) to the pons, in turn pressing a cellular "brake" (red) that reduces activity in the locus coeruleus (green). This removes a source of excitation from neurons (orange) that control muscles.

The cell loss in the amygdala also indirectly activates two circuits (pink and dark blue) in the pons that stimulate nerves in two areas of the medial medulla (yellow) that actively inhibit motor neurons. The result of the simultaneous loss of excitation and onset of inhibition in the motor neurons is a loss of muscle tone, causing the narcoleptic to fall.

Recent findings in narcoleptic dogs suggest that mutations in receptors for a neurotransmitter called hypocretin/orexin in the lateral hypothalamus can also cause cataplexy and the other symptoms of narcolepsy. The mutations may act by removing excitatory inputs (violet) to cells that maintain muscle tone and arousal and by triggering the





ELECTRICAL RECORDINGS (left) taken from the brain and neck muscles of a dog with narcolepsy show that cells in the locus coeruleus are inactive during the muscle paralysis of a cataplexy attack, whereas those in the medial medulla are active. The brain recordings (blue) were obtained using tiny

electrodes; the muscle ones (red), with an electromyograph. The unusual activity patterns may result from the degeneration of cells in the amygdala: a slice from the amygdala of a dog (right) shows multiple gaps in the axons (black streaks) that normally extend from one nerve cell to another.

ter variously called hypocretin or orexin. Neurotransmitter receptors sit on the surfaces of neurons like molecular locks. When a neurotransmitter "key" binds to its receptor, it sets off a chain reaction of chemical processes within the receiving cell that prompts the cell to take some action, such as sending its own neurotransmitter signal to a third cell. Mignot's group found that the mutation harbored by the narcoleptic dogs produces hypocretin/orexin receptors that are missing a critical part, so that they cannot respond normally to the messages they receive.

In a complementary study, researchers led by Masashi Yanagisawa of the Howard Hughes Medical Institute at the University of Texas Southwest Medical Center in Dallas have generated mice whose neurons cannot send the hypocretin/orexin message in the first place. They have observed that such mice also have some symptoms of narcolepsy, including REM sleep at sleep onset.

Hypocretin/orexin is made only in a region deep in the brain called the hypothalamus, which besides regulating body weight also controls water balance, pituitary functions, body temperature and many other processes. Hypocretin/orexin-producing neurons in the hypothalamus connect to other brain neurons that produce arousal, such as to the forebrain and brain-stem neurons that release acetylcholine and to other neurons that release histamine and serotonin. They are also linked up to brain-stem neurons, such as those in the locus coeruleus, that play an important role in the control of muscle tone.

Mutations that affect the hypocretin/orexin system might be responsible

for some cases of narcolepsy in humans, but it is unlikely that most human narcoleptics have mutations in the genes responsible for synthesizing hypocretin/orexin or its receptor. Most narcoleptics have no narcoleptic relatives, and the disease does not arise until the second or third decade of life. In addition, in 75 percent of cases in which narcolepsy occurs in an identical twin, the other twin is unaffected. These findings indicate that environmental conditions are important in human narcolepsy. These environmental conditions may cause damage to the hypocretin/orexin system, mimicking the symptoms caused by mutations, or may prompt damage to closely linked systems of neurons.

An Autoimmune Disease?

Some scientists have proposed that narcolepsy arises when unknown agents in the environment spur an autoimmune reaction that winds up damaging neurons in the brain circuits that control arousal and muscle tone. In 1984 Yutaka Honda and his colleagues at Seiwa Hospital in Tokyo found that all members of a group of 135 Japanese narcoleptics had one aspect of their tissue type in common, which meant their immune systems used the same molecule, one of the human leukocyte antigens (HLAs), to tell friend from foe. The molecule the narcoleptics shared was found in approximately 35 percent of nonnarcoleptic Japanese. Whereas the HLA type was clearly not sufficient to induce narcolepsy, Honda's finding indicated that HLA type greatly affected susceptibility to the disease. HLA molecules are pitchfork-shaped

structures that cells of the body use to show pieces of the proteins they contain to the immune system. Cells of the immune system ordinarily attack foreign substances and cells infected by viruses, which hijack cells into making viral proteins instead of normal ones.

Someone's HLA type is often referred to as their tissue type because people with the same HLA profile can receive tissue or organ transplants from one another. Certain autoimmune diseases tend to afflict those with particular HLA types, most likely because those HLA types when linked to particular antigens may look like naturally occurring proteins in the body, thereby causing the immune system to become confused and to damage normal cells.

The obvious next step will be to determine whether the immune systems of narcoleptics are mistakenly targeting the hypocretin/orexin receptors in their own brains as foreign. Because the body would continue to regenerate the receptors, such an autoimmune response would be expected to continue for the duration of the disease, but no such response has yet been detected in people with narcolepsy.

In another scenario the autoimmune response might be destroying the neurons or the parts of neurons that bear the hypocretin/orexin receptors, so that the autoimmune response would cease. Alternatively, the deficit in human narcolepsy could occur farther along the neuronal circuits regulating sleep than those cells involved in the hypocretin/orexin system. Autoimmune damage to neurons or receptors in the locus coeruleus or in other sleep-related regions of the brain might produce the syndrome even though the

hypocretin/orexin neurons and their receptors were functioning normally.

Evidence for an autoimmune cause of narcolepsy will most likely come from studies of the brains of people who had the disorder. Ever since French physician Jean Baptiste Edouard Gelineau named narcolepsy as a distinct syndrome in 1880, researchers have examined the brains of patients in a futile search for neurological damage that could explain the symptoms of the disease. In a series of studies in the 1980s and 1990s, Mignot, Dement and their Stanford colleagues Ted L. Baker and Thomas S. Kilduff observed that the brains of narcoleptic dogs had more than the usual number of receptors for the neurotransmitters acetylcholine, dopamine and norepinephrine and higher levels of some of the neurotransmitters themselves.

In the early 1990s Michael S. Aldrich of the University of Michigan noted similar changes in the brains of human narcoleptics. Such alterations in neurotransmitter and receptor levels, however, can result from behavioral changes—including sleep disturbances—so it has been unclear if they are the cause or the result of the disease.

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My colleagues and I considered this issue and wondered whether pathologists had failed to find consistent evidence for brain damage in narcoleptics because they had been looking at the wrong time in the disease process. Narcolepsy is a chronic disease but not a progressive one. After symptoms are fully established, narcoleptics do not get progressively worse or markedly better. This suggests that the damage might occur during a short time, roughly during the period in which a patient first develops signs of the illness. Debris left over from degenerative processes that occurred at the age of 20 would be re-

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before most patients died, and any remaining clues would be obscured by the normal degeneration of aging. A loss of neurons would be undetectable unless the dead cells were concentrated in a particular area, as in Parkinson's disease, or unless many, many neurons died, as in Alzheimer's disease.

Accordingly, my co-workers and I examined the brains of narcoleptic dogs shortly after their symptoms had begun. Using a stain that detects damaged neurons, we found clear evidence that neurons in certain areas of the dogs' brains were degenerating between one and two months of age—just before and during the onset of symptoms. Evidence of the degeneration largely disappeared by the time the dogs were six months old.

The degeneration in the dogs was most pronounced in the amygdala, a brain structure known to be involved in emotion and in inducing sleep, and adjacent

normality in the hypocretin/orexin receptor trigger the damage? Is it possible to prevent or even reverse the damage?

Until we can find answers, all we can offer people with narcolepsy are drugs to control their symptoms. We can counteract some of the sleepiness experienced by narcoleptics using stimulants such as Ritalin and Cylert or amphetamines, which activate dopamine receptors to increase the overall level of arousal. Another drug, Provigil, whose mechanism of action is not clear, may act by stimulating hypocretin/orexin neurons and other neural populations in the hypothalamus that in turn activate brain arousal systems. The downside is that such drugs are effective only for short periods and can cause unpleasant side effects, such as agitation, dry mouth and anxiety.

To prevent the cataplectic attacks of narcolepsy, physicians can prescribe agents that increase the availability of

We have found the first evidence of neuronal degeneration in narcolepsy.

regions at the bottom of the forebrain. Remarkably, although the brain stem mediates some of the symptoms of narcolepsy, it showed no clear signs of degeneration. We hypothesize that damage to the amygdala and adjacent forebrain areas can cause the motor symptoms of narcolepsy by inappropriately activating brain-stem circuits that are undamaged, just as a properly functioning car can run out of control if the person inside steps on the accelerator at the wrong time.

As usual in science, our findings answered one question but generated even more. What causes the damage we observed in the amygdala and other forebrain regions in the young dogs? Is it the result of an autoimmune process, as suggested by the human study? Does the ab-

norepinephrine in the brain. These include monoamine oxidase inhibitors—which block the enzyme that destroys norepinephrine after it is released by neurons—and drugs such as Prozac, whose breakdown products activate norepinephrine receptors. Gamma hydroxybutyrate (GHB), whose mode of action is unclear, can also be effective against cataplexy.

Our newfound understanding of the processes underlying narcolepsy gives us reason to hope that new treatments that restore the imbalance in the hypocretin/orexin, norepinephrine and other neurotransmitter systems that control the sleep-wake cycle will improve treatment of this disease. We are entering a promising era in narcolepsy research.

The Author

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Further Information

ENCYCLOPEDIA OF SLEEP AND DREAMING. Edited by Mary A. Carskadon. Macmillan, 1993. SLEEP AND DREAMING. Alan Rechtschaffen and Jerome M. Siegel in *Principles of*

Neural Science. Fourth edition. Edited by Eric R. Kandel, James H. Schwartz and Thomas M. Jessell. McGraw-Hill, 1999. BRAINSTEM MECHANISMS GENERATING REM SLEEP. Jerome M. Siegel in *Principles*

and Practice of Sleep Medicine. Third edition. Edited by Meir H. Kryger, Thomas Roth and William C. Dement. W. B. Saunders, 2000. Links to additional articles can be found at www.bol.ucla.edu/~jsiegel on the World Wide Web.