BOSTON—The understanding of narcolepsy took a major leap forward with the discovery of the orexin system in the late 1990s. But that discovery was only the first piece of the puzzle. Since then, major advances have been made in dissecting the circuitry underlying narcolepsy symptoms, developments that have also helped illuminate the puzzle of sleep itself.

An overview of what is known, and still unknown, about the neurobiology of narcolepsy was provided here at the American Neurological Association annual meeting in October by Thomas Scammell, MD, one of field’s leading researchers.

The announcement of a new neurotransmitter, orexin (also called hypocretin), in 1998 was followed in 1999 by the discovery that narcolepsy was caused by a profound loss of orexin neurons. That discovery “broke the field open” for understanding the molecular pathways of the disease, said Dr. Scammell, associate professor of neurology at Harvard Medical School in Boston.

Orexin neurons are found only in the hypothalamus, making it “a very tidy system” for studying, he said. Most narcolepsy patients have only 5- to 10-percent of the normal number of neurons, a deficiency whose causes are unknown in most cases. The disorder is characterized by daytime sleepiness, fragmented sleep at night, hypnagogic hallucinations, sleep paralysis, and its most dramatic manifestation, cataplexy, a sudden brief episode of muscular weakness while awake, triggered by strong positive emotions.

“The big questions are, why does a loss of these cells cause a lifetime of sleepiness, and how do positive emotions trigger cataplexy?”

The picture that is developing, Dr. Scammell said, is that orexin is responsible not for directly driving wakefulness, but for stabilizing it in the face of the brain’s sleep-promoting system.

The model that Dr. Scammell said “is actually a very likely explanation” is that there are two systems in the brain, one promoting sleep, and one promoting wakefulness, with each able to turn the other off.

Among the big remaining questions is what accounts for the common comorbidities of obesity and heart problems in narcoleptic individuals. But the biggest question in the sleep field is still why we sleep.

Such “flip-flop switches” tend to be unstable, or “twitchy,” in the words of the sleep expert who moderated the session, Clifford Saper, MD, PhD, professor of neurology at Harvard Medical School.
Narcolepsy

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School and chief of neurology at Beth Israel Deaconess Medical Center in Boston. Orexin, which is active during wakefulness, prevents that twitchiness, he said, raising the “activation barrier” between the two states, allowing long periods of wakefulness, which in turn promote long periods of sleep.

Growing evidence indicates that a major target for orexin is the histamine-producing neurons in the tuberomammillary nucleus in the posterior hypothalamus. Recently, researchers in Dr. Scammell’s lab genetically disrupted the orexin receptor throughout the brain hypothalamus. Recently, researchers in Dr. Scammell’s lab genetically disrupted the orexin receptor throughout the brain hypothalamus. Recently, researchers in Dr. Scammell’s lab genetically disrupted the orexin receptor throughout the brain hypothalamus. Recently, researchers in Dr. Scammell’s lab genetically disrupted the orexin receptor. In mice, the animal can produce perfectly normal long bouts of wakefulness,” Dr. Scammell said. “Signaling through histamine neurons is not the only system that promotes wakefulness, but certainly seems to be sufficient.”

“The next experiment could locally delete orexin receptors from that same region, and ask does it make a very sleepy mouse, or can signaling through other regions compensate? There is a lot more to be done to tease out these important pathways, but this is a first step,” he said.

CATAPLEXY

Cataplexy is perhaps the most intriguing aspect of narcolepsy. “This is a great and puzzling question,” Dr. Scammell said. “Over 80 percent of narcolepsy patients say positive emotions trigger muscle paralysis, but this has received very little attention” in terms of research.

Modeling cataplexy in mice was initially challenging, since, unlike dogs (in which narcolepsy has also been studied), mice don’t readily display emotional signals. But through trial and error, Dr. Scammell discovered several reliable stimuli to trigger the mouse version of happiness: cage running, social interaction, and most reliably, chocolate. “Chocolate is an extraordinary trigger for cataplexy in mice, increasing it eight-fold,” he said.

Examination of the mouse brain indicated a prominent role for the amygdala during episodes of cataplexy, a finding first reported in dogs. “This caught our eye, because this is part of the limbic system, and is involved in emotional processing. We tend to think of the amygdala as involved in negative aspects, such as fear,” he said, “but there is good imaging data that it is also involved in positive aspects.”

He found that without the chocolate stimulus, the drug had little effect in narcoleptic mice; but in the presence of chocolate, orexin neurons are gone, this activation turns on the amygdala, and ultimately leads to atonia. “That’s a key part of the emotional trigger.”

So far, Dr. Scammell said, pharmaceutical companies have had no success developing orexin agonists for treatment of narcolepsy (Antagonists have been developed, and one is currently before the FDA for use as a sleeping pill.) Narcolepsy can be treated with sodium oxybate, which triggers sleep and reduces daytime sleepiness, as well as cataplexy.

Much remains to be learned despite this important progress, according to Dr. Saper. Among the big remaining questions, he said, is what accounts for the common comorbidities of obesity and heart problems in narcoleptic individuals. But the biggest question in the sleep field is still why we sleep, he said. It is clear that it is important for memory consolidation, “but the mechanism of how and why sleep should promote that is not understood.”

FOR FURTHER READING:

Dr. Thomas Scammell proposed that if the amygdala is responsible for triggering cataplexy brought on by positive emotions, then lesioning it should reduce cataplexy. And this is indeed what he found.

Dr. Clifford Saper said that orexin, which is active during wakefulness, prevents the flip-flop switches between the brain systems promoting sleep and wakefulness. It raises the ‘activation barrier’ between the two states, allowing long periods of wakefulness, which in turn promote long periods of sleep.

Dr. Thomas Scammell: “The next experiment could focusally delete orexin receptors from that same region, and ask does it make a very sleepy mouse, or can signaling through other regions compensate? There is a lot more to be done to tease out these important pathways, but this is a first step.”