‘On-Off’ Switches Shed Light on Brain Disorders

Narcolepsy, cataplexy, and REM sleep behavior disorder linked to errant ‘flip-flop’ mechanisms.

BY BETSY BATES

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SAN DIEGO – A series of “on-off” switches regulates sleep, clarifying many of the mechanisms underlying narcolepsy, cataplexy, and REM sleep behavior disorder, according to Dr. Clifford B. Saper.

The states of sleep and wakefulness and rapid eye movement and non-REM sleep can best be understood as “flip-flop” mechanisms of brain circuitry, akin to light switches, said Dr. Saper, professor of neurology and neuroscience at Harvard Medical School and head of the department of neurology at Beth Israel Deaconess Medical Center in Boston.

“Each side inhibits the other” in an ascending arousal pathway to the cortex, facilitating rapid transitions from one state to the other.

Normally, human beings spend 99% of the 24-hour day fully awake or fully asleep, and just 1% of the time transitioning. This is due to an on-off switch that regulates arousal and sleep, Dr. Saper said at the meeting.

“One of the problems with a flip-flop switch is that it has a tendency, sometimes, to fall into the wrong position too easily. One can imagine driving down a boring road and flipping into the wrong state and suddenly being asleep behind the wheel of a car,” he said.

To prevent such an occurrence, the brain stabilizes wakefulness by the use of orexins, or hypocretins, which are neuropeptides produced by excitatory neurons in the lateral region of the hypothalamus.

Narcolepsy, in which patients do fall asleep essentially at the “flip of a switch,” is the result of a single neurotransmitter deficit in sleep’s “master switch,” the ventrolateral preoptic nucleus, Dr. Saper explained.

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DR. SAPER

A similar “flip-flop” switch regulates the normally rapid transition between REM and non-REM (slow-wave) sleep, he said.

The development of REM sleep behavior disorder (in which patients make jerky motor maneuvers as they act out dreams during sleep) and cataplexy – atonic lapses in muscle control from a waking state – are opposites on a spectrum, both indicative of triggering of the on-off mechanism at an inappropriate point in the cycle.

Of great interest to Dr. Saper is an evolving apparent link between the development of REM sleep behavior disorder in young adulthood and later development of Parkinson’s disease, a phenomenon that occurs in about half of REM behavior disorder patients within 12 years.

He noted that Dr. Ronald B. Postuma and his associates at Montreal General Hospital have identified early markers of Parkinson’s disease in idiopathic REM sleep behavior disorder patients, including difficulties with visual and olfactory discrimination tasks and subthreshold but low scores on the Unified Parkinson’s Disease Rating Scale.

The connection has led some researchers to suspect that synucleinopathies such as Parkinson’s disease and dementia with Lewy bodies may begin at the brainstem level of the locus coeruleus or the subcoeruleus complex and slowly progress in an ascending pathway to the basal ganglia over years or decades, offering the possibility of introducing neuroprotective therapy to stop that progression.

Dr. Saper reported having no relevant financial disclosures. ■