Orexin Levels in the Brain
Reveal Clues to Excessive Sleepiness

Traumatic brain injury (TBI) is a major cause of death and disability, especially among young people. A total of 5.3 million Americans, or 2% of the U.S. population, currently live with disabilities resulting from TBI, and this number continues to grow in light of recent world events. Studies show a high prevalence (up to 72%) of sleep-wake disturbances in the TBI population including post-traumatic hypersomnia and narcolepsy-like symptoms, which can persist as long as 3 years after injury. However, effective therapeutics are still lacking. Strategies that target both short-term and long-term cognitive impairments are urgently needed.

A chemical in the brain known as orexin (also known as hypocretin-1) may be dysregulated after traumatic brain injury. Orexin has been shown to be important for the regulation of arousal and wakefulness. This peptide neurotransmitter is absent from the cerebrospinal fluid (CSF) of patients with narcolepsy, a disorder which causes fragmented sleep as well as excessive daytime sleepiness. Intriguingly, orexin is also significantly decreased in the CSF in patients after TBI. In addition, patients with TBI show significant loss of orexin neurons in the hypothalamus at autopsy.

M. Iranda M. Lim, M.D., Ph.D., a clinical sleep fellow at the Penn Sleep Center, has collaborated with Jon T. Willie, M.D., Ph.D., a neurosurgery resident, and David L. Brody, M.D., Ph.D., an assistant professor in neurology at Washington University in St. Louis, to develop a mouse model of TBI in which orexin levels could be measured in the brain. Dr. Lim recently won the Narcolepsy Section Investigator Award from the American Academy of Sleep Medicine for her abstract detailing these findings, entitled “Dysregulation of Brain Orexin and Arousal in a Mouse Model of Traumatic Brain Injury.”

This work was presented at the Associated Professional Sleep Societies (APSS) meeting in Minneapolis, MN on June 14, 2011. Mice were implanted with microdialysis cannulas which allowed for the serial collection of brain interstitial fluid every 90 minutes for the quantification of orexin levels. Intracerebral microdialysis is a powerful tool that can be used easily and is adaptable from animal models to humans, and therefore facilitates translational studies. Orexin levels were tracked both pre- and post-TBI in mice, and found to be significantly suppressed after TBI compared to baseline values. In addition, mice slept more and showed less locomotor activity after TBI. This mouse model validates findings found in patients with TBI and is the first to show a direct, causal relationship between TBI and orexin dysfunction. Future experiments are planned to examine orexin-based therapeutics with the hope of improving clinical outcomes such as excessive sleepiness and cognitive dysfunction after TBI.

Oral presentations focused on four areas of sleep research: Neural Mechanisms of Sleep and Wake, Assessment and Consequences of Sleep Loss, Causes and Consequences of Disordered Sleep, and Genetics of Sleep and Sleep Mechanisms. Similar topics in basic and clinical sleep research were explored in a wide range of poster presentations.

At the conclusion of the retreat, several trainees were recognized for outstanding presentations. Matthew Nelson (Department of Neurology) who spoke on “Behavioral quiescence in C. elegans is regulated by the FFP, Par-30, cep-12, and ceh-52” received the award for best talk. Recipients of best poster awards included Adrian Dijkstra (Unit for Experimental Psychiatry) for “Photoperiodic effects of circadian workload on sleep”; Christine Kuhl (Center for Sleep and Circadian Neurobiology) for “Effects of the clock and acute sleep deprivation on fatty-acid binding protein expression in murine brain”; and Hillery McCarren (Pharmacology Graduate Group) for “Optogenetic manipulation of the ventral striatal preoptic area to explore its role in anesthetic sensitivity.”

Dr. Phil Gehman, Assistant Professor of Psychology in the Department of Psychiatry and clinical director of the behavioral sleep medicine program received the Samuel T. Kuna Excellence in Mentoring award for his work with trainees.
Individual Differences in Response to Sleep Loss

The following article has been prepared for the Penn Sleep Newsletter by Namni Goel, PhD, Research Associate Professor of Psychology in Psychiatry, Division of Sleep and Chronobiology, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania.

Individual Differences in Response to Sleep Loss

The majority of the patients originally described by Dr. Stunkard were women with refractory obesity. They exhibited a high caloric intake between dinner and bedtime and a lower caloric intake in order to consume food. A according to current diagnostic criteria, individuals with night eating syndrome consume at least 25% of their total daily caloric intake – predominantly carbohydrates – between evening and bedtime, and awaken to eat at least twice weekly. They are aware of their eating behaviors. Based on the observation that patients with night eating syndrome do not demonstrate the expected nocturnal rise in melatonin and leptin, Stunkard and others have postulated that there may be a neuroendocrine mechanism underlying this disorder.

In contrast to night eating syndrome, patients who have what has been designated as “sleep-related eating disorder” are often unaware of their nocturnal behavior. They arise from bed, usually in the first third of the night, with an apparent compulsion to eat. Their recall of these activities is limited, and the assessment of sleep-related eating disorder may be based on observations of food in the kitchen or bedroom the following morning. There is a preference for high calorie foods; however, because of their limited awareness, patients may eat raw food or substances that are inedible such as cardboard or pet food. Patients with sleep-related eating disorder appear to be in a dissociated state analogous to the mixed state of sleep and wakefulness exhibited by sleepwalkers. There is in fact a high prevalence of sleepwalking in this group.

In clinical practice, patients are encountered whose nocturnal eating shares some features of both disorders, suggesting a degree of diagnostic overlap. Treatment can be challenging. Both sertraline and topiramate have been helpful in patients with night-eating syndrome. Sleep-related eating disorder has also been successfully treated with topiramate, as well as with clonazepam and dopaminergic agents. Co-sleeping with patients with sleep-related eating disorders such as apneas or restless legs syndrome which predispose to partial arousals should also be treated, and medications which have been implicated in provoking parasomnias, such as zolpidem, should be discontinued.

Additional information about the various forms of nocturnal eating can be obtained at the American Academy of Sleep Medicine website (http://yoursleep.aasmnet.org) for evaluation of unusual behaviors during sleep, contact the Penn Sleep Center at 215-662-7772.