October 13, 8:40- 9:40 Plenary Lecture

Deciphering the mystery of sleep: toward the molecular substrate for sleepiness

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Although sleep is a ubiquitous behavior in animal species with central nervous systems, the neurobiology of sleep remain mysterious. Our discovery of orexin, a hypothalamic neuropeptide involved in the maintenance of wakefulness, has helped reveal neural pathways in the regulation of sleep/wakefulness. Orexin receptor antagonists, which specifically block the endogenous waking system, have been approved as a new drug to treat insomnia. Also, since the sleep disorder narcolepsy-cataplexy is caused by orexin deficiency, orexin receptor agonists are expected to provide mechanistic therapy for narcolepsy; they will likely be also useful for treating excessive sleepiness due to other etiologies.

Despite the fact that the executive neurocircuitry and neurochemistry for sleep/wake switching has been increasingly revealed in recent years, the mechanism for homeostatic regulation of sleep, as well as the neural substrate for "sleepiness" (sleep need), remains unknown. To crack open this black box, we have initiated a large-scale forward genetic screen of sleep/wake phenotype in mice based on true somnographic (EEG/EMG) measurements. We have so far screened >10,000 heterozygous ENU-mutagenized founders and established a number of pedigrees exhibiting heritable and specific sleep/wake abnormalities. By combining linkage analysis and the next-generation whole exome sequencing, we have molecularly identified and verified the causal mutations in several of these pedigrees. Biochemical and neurophysiological analyses of these mutations are underway. Indeed, through a systematic cross-comparison of the Sleepy mutants (with a gain-of-function change in a serine/threonine kinase pathway) and sleep-deprived mice, we have found that the cumulative phosphorylation state of a specific set of mostly synaptic proteins may be the molecular substrate of sleep need.