Title: Towards the Mysteries of Sleep

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Abstract

Although sleep is a ubiquitous behavior in animal species with well-developed central nervous systems, many aspects in the neurobiology of sleep remain mysterious. Our discovery of orexin, a hypothalamic neuropeptide involved in the maintenance of wakefulness, has triggered an intensive research examining the exact role of the orexinergic and other neural pathways in the regulation of sleep/wakefulness. The orexin receptor antagonist suvorexant, which specifically block the endogenous waking system, has recently been approved as a new drug to treat insomnia. Also, since the sleep disorder narcolepsy is caused by orexin deficiency, orexin receptor agonists are expected to provide mechanistic therapy for narcolepsy; they will likely be 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," 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 >7,000 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 mutation in several of these pedigrees. Biochemical and neurophysiological analyses of these mutations are underway. Since these dominant mutations cause strong phenotypic traits, we expect that the mutated genes will provide new insights into the elusive pathway regulating sleep/wakefulness.