

KVA-JSPS lecture about orexins

Deciphering the mysteries of sleep: toward the molecular substrate for “sleepiness”

Prof. Masashi Yanagisawa, MD, PhD

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Time: Wednesday 2nd October 2024 at 16:00

Lecture will follow after a short presentation of JSPS

Place: H:son Holmdahlsalen, Entrance 100, Akademiska sjukhuset

The lecture is possible thanks to a grant from
JSPS, the Japan Society for Promotion of Science

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Please contact Prof. Larhammar if you wish to meet with
Prof. Yanagisawa during his visit to Uppsala



Deciphering the mysteries of sleep: toward the molecular substrate for “sleepiness”

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Although sleep is a ubiquitous behavior in animal species with a nervous system, many aspects in the neurobiology of sleep remain mysterious. Our discovery of orexin, a hypothalamic neuropeptide involved in the maintenance of wakefulness, has triggered intensive research examining the exact role of the orexinergic and other neuronal pathways in the regulation of sleep/wakefulness. Orexin receptor antagonists, which specifically block the endogenous waking system, have been approved as a new strategy 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 the disease; they will likely be also useful for treating excessive sleepiness due to other etiologies.

Even though the executive neurocircuitry and neurochemistry for sleep/wake switching, including the orexinergic system, has been increasingly revealed in recent years, the mechanism for homeostatic regulation of sleep, as well as the neural substrate for “sleepiness” (sleep pressure), 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 several 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. 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. Indeed, through a systematic cross-comparison of the SIK3 *Sleepy* mutants and sleep-deprived mice, we have found that the cumulative phosphorylation state of a specific set of mostly synaptic proteins may represent the molecular substrate of sleep pressure. We have also found that the neuronal molecular pathway LKB1-SIK3-HDAC4/5 may represent the level of sleep pressure, regulating the amount, depth, and timing of sleep by acting in different brain regions, respectively (Kim et al. *Nature* 612: 512-518, 2022; Zhou et al. *Nature* 612: 519-527, 2022).

Prof. Yanagisawa received his PhD at the University of Tsukuba where he discovered the powerful vasoconstrictor peptide endothelin. His group later identified a receptor for endothelin which is now an important target for treatment of hypertension. After moving to Texas Southwestern Medical Center in Dallas he identified the endothelin-converting enzyme and later described the role of the endothelin pathway in embryonic development.

His project to deorphanize G protein-coupled receptors resulted in the discovery of the hypothalamic neuropeptide orexin in 1998. The year after, he showed that the sleep disorder narcolepsy is caused by orexin deficiency. This knowledge has resulted in orexin receptor antagonists approved for treatment of insomnia. An ongoing project in Tsukuba has led to identification of several new genes and molecular pathways that are importantly involved in the regulation of sleep amounts and the level of sleep need.

Prof. Yanagisawa has received numerous honours and awards, most recently the Breakthrough Prize in Life Sciences. He was elected to the U.S. National Academy of Sciences in 2003. Since 2012 he is the director for the International Institute for Integrative Sleep Medicine at the University of Tsukuba.