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Prof. Dr. Hans-Peter Landolt[1,2]
[1]Institute of Pharmacology and Toxicology, University of Zürich, Zürich, Switzerland
[2]Zürich Center for interdisciplinary Sleep Research, University of Zürich, Zürich, Switzerland

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Elucidating mechanisms of sleep-wake regulation in humans with pharmaco-genetic tools

Sleep-wake disorders are highly prevalent in society. The normal alternation between sleep and wakefulness is tightly regulated, and sleep-wake states reflect highly complex behaviors. Little is known about the molecular underpinnings of physiological sleep-wake regulation and functions. For the development of rational treatment of disturbed sleep and wakefulness, a molecular understanding of sleep-wake regulatory processes is indispensable. Important aspects of sleep-wake regulation in animals and humans are genetically controlled and, thus, must have a molecular basis. Consistent with this view, the combination of neurophysiologic, genetic and pharmacologic tools revealed specific roles for adenosine, dopamine and glutamate receptors and metabolic pathways in sleep-wake regulation. These studies also showed that functional allelic variation in candidate genes can profoundly affect functional aspects of sleep and wakefulness, even in healthy humans and under physiological conditions, as well as modulate individual responses to hypnotic and wake-promoting agents. These insights may lead to a rationale for personalized sleep-wake pharmacotherapy (Holst et al., *Annu Rev Phamacol Toxicol*, 2016). In the future, together with novel 'omics'-studies of sleep in health and disease, they may pave the way for the discovery of new evidence-based treatments of sleep-wake pathologies such as insomnia and the pharmacological enhancement of sleep-associated brain functions such as neuronal plasticity.