Systems Biology of Mammalian Sleep/Wake Cycles ～Phosphorylation Hypothesis of Sleep～

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The detailed molecular and cellular mechanisms underlying NREM sleep (slow-wave sleep) and REM sleep (paradoxical sleep) in mammals are still elusive. To address these challenges, we first constructed a mathematical model, Averaged Neuron Model (AN Model), which recapitulates the electrophysiological characteristics of the slow-wave sleep. Comprehensive bifurcation analysis predicted that a Ca^{2+}-dependent hyperpolarization pathway may play a role in slow-wave sleep. To experimentally validate this prediction, we generate and analyze 26 KO mice, and found that impaired Ca^{2+}-dependent K^+ channels (*Kcnn2* and *Kcnn3*), voltage-gated Ca^{2+} channels (*Cacna1g* and *Cacna1h*), or Ca^{2+}/calmodulin-dependent kinases (*Camk2a* and *Camk2b*) decrease sleep duration, while impaired plasma membrane Ca^{2+} ATPase (*Atp2b3*) increases sleep duration. Genetical (*Nr3a*) and pharmacological intervention (PCP, MK-801 for *Nr1/Nr2b*) and whole-brain imaging validated that impaired NMDA receptors reduce sleep duration and directly increase the excitability of cells. Based on these results, we propose **phoshporylation hypothesis of sleep** that phosphorylation-dependent regulation of Ca^{2+}-dependent hyperpolarization pathway underlies the regulation of sleep duration in mammals. We also recently developed a simplified mathematical model, Simplified Averaged Neuron Model (SAN Model), which uncover the important role of K^+ leak channels in NREM sleep. In this talk, I will also describe how we identify essential genes (*Chrm1* and *Chrm3*) in REM sleep regulation, and propose a plausible molecular definition of a paradoxical state of REM sleep.