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Kinase signalling pathway regulates sleep quality and quantity

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Abstract

Sleep is homeostatically regulated, yet the underlying biological mechanisms regulating sleep need remain largely elusive. In prior research, we identified the kinase SIK3 as a crucial component in sleep homeostasis via EEG/EMG-based screening of randomly mutated mice. A splice mutation in the Sik3 gene was found to result in an augmentation of NREMS. Subsequently, we revealed that distinct populations of excitatory neurons regulate sleep quantity and quality through neuron type- and brain region-specific manipulation of gain-of-function and loss-of-function mutants of the Sik3 gene. Furthermore, a forward genetic study led to the identification of HDAC4 as a sleep-regulating molecule. Genetic, biochemical, and histological analyses indicate that SIK3 phosphorylates HDAC4, thus enhancing sleep. Single nucleus RNA-seq analysis disclosed the expression of several candidate genes in cortical excitatory neurons that link SIK3-HDAC4 signaling to network-level alterations.

References

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Kinase signalling in excitatory neurons regulates sleep quantity and depth. ***Nature*** 612, 512-518, 2022

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