Study in mice pinpoints molecular basis of deep sleep, suggests avenues for novel treatments

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Healthy sleep is a basic physiologic need. In its absence, a myriad of processes in the body can go terribly awry. Chronic sleep problems have

been linked to mental health disorders, cardiovascular disease, type 2 diabetes, and obesity, among other conditions.

Yet, consistently achieving the deep, restorative sleep necessary for optimal physiologic health and peak cognitive performance can be difficult due to lifestyle, environmental, and biologic factors.

One of the most confounding questions in sleep biology has been how deep sleep is regulated by the brain. The answer could help illuminate new ways to mitigate sleep problems.

Now, a newly published study led by Harvard Medical School researchers at VA Boston Healthcare Systemoffers critical clues into this longstanding mystery.

The work, conducted in mice and published April 26 in *Nature Communications*, identifies an area in the brain that regulates the oscillations of delta waves—electrical signals transmitted across neurons that arise during the deepest phases of relaxation. They are a hallmark of restorative sleep.

The research team homed in on neurons in the thalamus, a region of the brain that regulates sleep and wakefulness, among other functions. Using CRISPR-Cas9 gene editing, the researchers disrupted a gene that codes for a protein that binds the inhibitory neurotransmitter GABA. The protein is a target of drugs that promote sleep. Disruption of this gene in mouse models boosted the activity of delta waves and enhanced deep sleep in the animals.

If replicated in further animal models, the findings could lay the groundwork for designing therapies that precision-target this protein to induce deep sleep.

"Our findings represent an important step forward in pinpointing the molecular basis of sleep regulation and point to an alternative pharmacologic strategy for promoting natural, restorative sleep," said study senior investigator Radhika Basheer, associate professor of psychiatry at HMS and VA Boston.

New therapies are sorely needed. Commonly used insomnia medicines, while an important tool for treatment of persistent insomnia, have well-known drawbacks. Many of these medications work by getting people to fall asleep fast, but they also tend to dampen the activity of restorative delta waves. Thus, while such medications promote falling asleep, the slumber they induce is not necessarily restorative.

"We believe our findings set the stage for developing a new class of sleep medicines that can achieve this all-important maintenance of deep sleep by boosting delta wave oscillations," added Basheer, who co-led the study with colleague Ritchie Brown, associate professor of psychiatry at HMS.

More information: David S. Uygun et al, Knockdown of GABAA alpha3 subunits on thalamic reticular neurons enhances deep sleep in mice, *Nature Communications* (2022). DOI: 10.1038/s41467-022-29852-x

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