New sleep molecule discovered: 'It shows just how complex the machinery of sleep is'

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When brain scientist Birgitte Kornum from the Department of Neuroscience recently arrived in Rome for one of the largest sleep conferences in the world, she was completely taken aback. There were

pharmaceutical companies everywhere—with stands, information material and campaigns.

They all wanted to treat daytime sleepiness or to turn off the brain at night. And a lot of them focused on hypocretin, which is a protein found in brain cells and which has recently attracted a lot of attention within sleep research.

This is because hypocretin is suspected to play a role in both insomnia, which is a decreased ability to fall asleep at night, and in narcolepsy, which is a decreased ability to stay awake during the day. People suffering from insomnia may have too much hypocretin in the brain, while people suffering from narcolepsy have too little. Researchers also suspect hypocretin to play a role in depression, ADHD and other mental disorders.

A lot is already known about the hypocretin system in the brain. There is even a new drug for insomnia countering the effect of hypocretin, latest introduced in Canada in 2018. According to Birgitte Kornum, though, the problem is that we know very little about how hypocretin is regulated inside the cells.

Therefore, Associate Professor Birgitte Kornum and her colleagues set out to shed light on the issue in a new study, which has recently been published in the journal *PNAS*. The study combines tests on mice, zebrafish and human cells, and the researchers cooperated with their neighbors at the University of Copenhagen's Department of Cellular and Molecular Medicine, among others.

MicroRNA associated with sleep regulation

The team of researchers have spent several years studying one of the cellular mechanisms that affect hypocretin levels. Here they have

focused on a small molecule called microRNA-137 (miR-137).

"We discovered that miR-137 helps regulate hypocretin. To experience normal sleep, you need to have the right amount of hypocretin in the brain at the right time, and miR-137 helps with that. Though MiR-137 is also found in other parts of the body, it is especially pronounced in the brain," Birgitte Kornum says about the new study, which she has headed together with Assistant Professor Anja Holm from Aalborg University.

MicroRNA regulates various cellular processes, including hypocretin levels. Therefore, there is considerable research interest in microRNAs, as they could be targeted in order to regulate such processes.

Previously, the scientists knew very little about the role played by miR-137 in the brain, but now Birgitte Kornum's research team has demonstrated that it is associated with hypocretin regulation and thus with sleep.

"This is the first time a microRNA is associated with sleep regulation. Drawing on the UK Biobank, we discovered some genetic mutations in miR-137 which cause daytime sleepiness. The study demonstrates this connection in both mice and zebrafish, and we are able to prove the connection with hypocretin. Our discovery shows just how complex the machinery of sleep is. Imagine inheriting a variant of miR-137 that puts you at higher risk of feeling sleepy during the day," says Birgitte Kornum.

Hypocretin affects sleep stages

Hypocretin, which has caught the attention of the pharmaceutical companies, also affects the order of the sleep stages.

Our sleep is usually divided into four stages. The stages follow a specific

order, and this order is vital to the quality of our sleep.

"Narcolepsy patients suffering from low levels of hypocretin experience muddled sleep stages. We know this from mice tests demonstrating that hypocretin affects the order of these stages," explains Anja Holm from Aalborg University, who is first author of the study and who did the tests together with Birgitte Kornum.

Existing research suggests that to solve the problem we need to gain more knowledge of hypocretin regulation. And here the Danish researchers point to a different, but equally important piece of the puzzle, namely the immune system.

"Most people know that when you are ill you often feel tired. And when you have a fever and the immune system is hard at work, you often suffer from poor sleep. So we know that something happens to the hypocretin level when the body is trying to fight off a virus infection, for example, and we are trying to understand this process," says Birgitte Kornum.

"In the study, we show that one of the immune system's transmitter substances, IL-13, has a special effect on hypocretin. We can tell that when we add IL-13, it affects miR-137 and thus also the level of hypocretin in the body. We still do not know why, though, but we are currently doing tests that may be able to give us an answer."

More information: Anja Holm et al, The evolutionarily conserved miRNA-137 targets the neuropeptide hypocretin/orexin and modulates the wake to sleep ratio, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2112225119

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