



"Scientists unlock key aspect of sleep chemistry"

Novel technology reveals regulation of melatonin

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Researchers at the [Johns Hopkins University](#) and National Institutes of Health have discovered a key step in how the body controls melatonin, the chemical that regulates the sleep-wake cycle.

The knowledge could eventually help scientists come up with drugs to better treat sleep disorders, including insomnia, narcolepsy and jet lag.

Published yesterday in the online edition of Nature Structural Biology, the paper identified the switch that destroys the enzyme controlling melatonin production.

"We've filled an important gap in our understanding of why melatonin levels rise and fall," said Hopkins pharmacologist Philip Cole, who led the study, along with Hopkins researcher Weiping Zheng.

In humans and most other animals, melatonin largely controls the sleep-wake cycle. At night, the chemical increases in key areas of the brain; in daylight, it decreases.

Cole and his colleagues studied an enzyme called arylalkylamine N-acetyltransferase (AANAT), which plays a major role in turning serotonin into melatonin. When present, AANAT triggers melatonin production. In the presence of light, the body quickly destroys the enzyme, which ends melatonin production.

Until now, no one knew exactly how this destruction occurred.

Cole and his partners suspected that the enzyme broke down after losing sections made up of phosphates - a process known as de-phosphorylation.

To test the theory, they built a synthetic variant of the enzyme, from which the phosphates could not be removed. NIH neuroendocrinologist David Klein, another member of the research group, compared the modified enzyme to a car key that had been permanently installed in the ignition.

The researchers inserted these modified enzymes into Chinese hamster cells and found that even when exposed to light, the organism continued to pro-

duce melatonin. The results indicate that the phosphate controls the enzyme, the researchers concluded.

"It is revolutionary, because nobody before this knew how melatonin level was regulated," said Zhongsen Zhang, another Hopkins researcher who worked on the project.

Knowing how AANAT works, researchers can now look for chemicals to affect that process, either hastening the enzyme's demise or lengthening its life. These chemicals might end up as drugs for sleep disorders.

"This gives us a potential target for controlling levels of melatonin in the body," Cole said. The synthetic enzyme created by the researchers is not itself a good drug candidate, Cole said, because it doesn't penetrate the target organs well and because enzymes generally have immunological and other side effects.

The research could bear additional fruit because it was the first time that scientists have been able to create an enzyme that's impervious to phosphorylation. "We've used an absolutely novel technology here," Klein said.

Thousands of enzymes switch themselves on and off by adding or removing phosphate groups - some play key roles in diseases.

By using synthetic enzymes whose phosphates are permanently attached, scientists may be able to learn more about how these enzymes contribute to various ailments.

The new technique could be especially useful to cancer researchers, because they believe that many forms of cancer involve faulty phosphorylation - a process in which enzymes become stuck in the "on" mode.