Melatonin precursor stimulates growth factor circuits in brain

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Scientists at Emory University School of Medicine have discovered unexpected properties for a precursor to melatonin, the hormone that regulates sleep cycles.

Melatonin is produced from the neurotransmitter serotonin in a daily rhythm that peaks at night. Melatonin's immediate precursor, N-acetylserotonin, was not previously thought to have effects separate from those of melatonin or serotonin.

Now an Emory team has shown that N-acetylserotonin can stimulate the same circuits in the brain activated by the growth factor BDNF (brain-derived neurotrophic factor).

The results will be published online this week in the Proceedings of the National Academy of Sciences.

The team was led by Keqiang Ye, associate professor of pathology and laboratory medicine, and P. Michael Iuvone, professor of pharmacology and director of research at Emory Eye Center. Researchers from Morehouse School of Medicine and the University of Wisconsin contributed to the paper.

The discovery has implications for the study of how some antidepressants function and may also explain previous observations that N-acetylserotonin has antidepressant activity in animal models of depression.

"Our results suggest that the molecules and pathways involved in mood regulation and circadian rhythms are intertwined," Ye says.

A lack of BDNF, which pushes brain cells to grow and helps them resist stress, is thought to lie behind depression and several neurodegenerative diseases. Ye and his colleagues have been searching for chemicals that can mimic BDNF by activating TrkB, the receptor for BDNF on cells' surfaces.

Several widely prescribed antidepressants (selective serotonin reuptake inhibitors such as fluoxetine/Prozac) increase levels of serotonin in the brain, but the connections between serotonin levels and depression are complex. Because antidepressants seem to take weeks to display their effects, scientists have proposed that their real targets are BDNF and TrkB.

"We were exploring whether the serotonin system is involved in TrkB signaling," Ye says. "We were surprised to find that N-acetylserotonin, but not serotonin or melatonin, can activate TrkB."

N-acetylserotonin could stimulate TrkB even when BDNF was not present, both in cell culture dishes and in mice, Ye and his colleagues found. It could also protect neurons from overstimulation in the same way that BDNF can.

Melatonin is produced at several sites in the body: the pineal gland, the retina and the intestine. One of the most common strains of laboratory mice (C57Bl6) is deficient in making N-acetylserotonin and melatonin and develops retinal degeneration.

The authors observed that in the retinas of mice that produce adequate melatonin, TrkB is turned on at night, a pattern that matches the appearance of N-acetylserotonin. However, the pattern of TrkB activation is flat in C57Bl6 melatonin-deficient mice.

Ye's laboratory is now investigating the mechanism by which N-acetylserotonin activates TrkB. He says that N-acetylserotonin has a short lifetime in the body but similar compounds that are more stable may be useful in treating neurological diseases.

Provided by Emory University