Sleep deprivation increases serotonin 2a receptor response in brain

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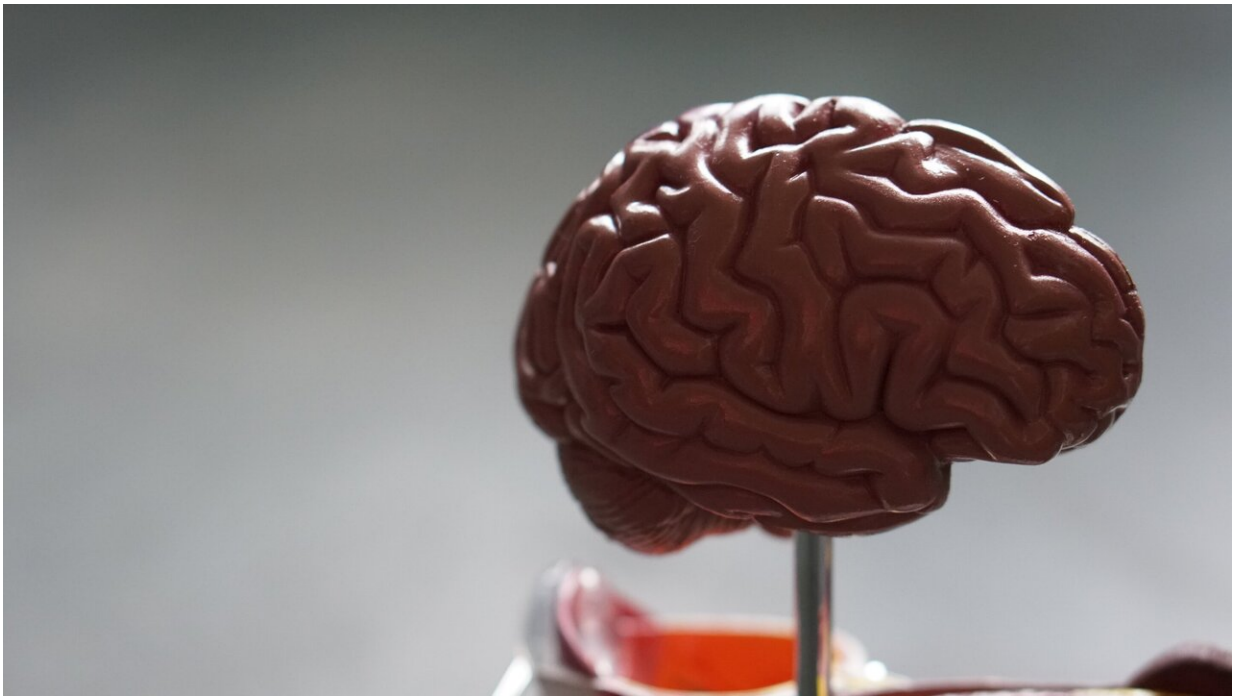

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The serotonin 2A (5-HT_{2A}) receptor is widely distributed in the brain and plays a critical role in perception, cognition and psychosis. It is also responsible for the psychedelic effects of drugs, such as psilocybin (hallucinogenic mushrooms) and LSD. Abnormal 5-HT_{2A} receptor function is associated with psychiatric disorders, including schizophrenia. The leading class of antipsychotic drugs used to treat

schizophrenia targets 5-HT_{2A} receptors to reduce symptoms of hallucinations and impaired cognition.

A study led by Amelia Gallitano, MD, Ph.D., professor in the Department of Basic Medical Sciences and Psychiatry at the University of Arizona College of Medicine—Phoenix, found that an environmental stressor, sleep deprivation, can significantly increase the levels of serotonin 2A neurotransmitter receptors in 6 to 8 hours in animal models. For individuals with schizophrenia, these findings suggest environmental stressors may alter the balance in brain receptors that are controlled by antipsychotic drugs.

"Our study shows it is possible for environmental stimuli to change the levels of receptors that have important roles in the brain—in a matter of hours," said Gallitano, whose lab focuses on investigating the interaction of environmental stress and genetic predisposition in the development of psychiatric illnesses. "Now we think we know the mechanism through which this happens; it's through the gene EGR3."

Signaling mechanism

The role of 5-HT_{2A} receptors in controlling one's ability to understand and process information has been extensively studied. However, the signaling process that regulates this gene expression has remained poorly understood—until now.

Receptor proteins on the surface of brain cells control the internal communication network of the brain. These receptors are created when a gene (a region of DNA) is turned on and produces the instructions (messenger RNA) that the cell uses to create the protein, in this case the 5-HT_{2A} receptor. How many of the receptors are made, and present on the cell surface, determines how the brain cell responds to the neurotransmitter serotonin, and also to drugs that bind to the receptor,

such as antipsychotics, LSD and psilocybin.

The 5-HT_{2A} receptor receives its encoded instruction from the HTR2A gene. The study revealed that proteins produced by EGR3, an early growth response gene, also were required for expression of the 5-HT_{2A} receptor.

The function of EGR3 is to bind to DNA and turn on and off other genes. The findings showed stimuli caused by sleep deprivation triggered EGR3 to bind to the 5-HT_{2A} receptor gene and turn on its production of mRNA instructions to make more protein. This resulted in more 5-HT_{2A} receptors present in the brain within several hours.

Consequences for schizophrenia

The findings from this study enhance understanding of how environment alters expression of brain receptors that mediate prefrontal cortex function. Activity in the prefrontal cortex region of the brain is essential for spatial reasoning and working memory. Dysfunction in this area may contribute to the cognitive deficits that characterize schizophrenia.

Schizophrenia is a mental illness characterized by abnormalities in perception, thinking and memory. The illness disrupts cognition, sleep and memory processes, causing patients to experience hallucinations and disassociation from reality.

In the search for treatments for severe psychiatric symptoms, drugs that initiate a physiological response by binding to 5-HT_{2A} receptors are experiencing a resurgence. The fact that5-HT_{2A} receptors mediate the hallucinogenic effects of drugs, such as LSD and psilocybin, suggests this receptor may influence the hallucinations and perceptual disturbances of schizophrenia.

"We want to understand the genes that get expressed as a result of environmental stimuli and how that gene-environment interaction influences behavioral changes that can give rise to mental illness symptoms," Gallitano said.

The findings were published in *Molecular Psychiatry*.

More information: Xiuli Zhao et al, Acute sleep deprivation upregulates serotonin 2A receptors in the frontal cortex of mice via the immediate early gene Egr3, *Molecular Psychiatry* (2022). DOI: 10.1038/s41380-021-01390-w

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