

## Light-Activated Drugs Targeting Adenosine A<sub>2A</sub> Receptors in the Brain that Induce Sleep

Adenosine A<sub>2A</sub> receptors (A<sub>2A</sub>R) in the nucleus accumbens of the brain play an important role in regulating sleep and motivation, but until now, no drugs have been able to selectively modulate their function without affecting other organs or brain areas. In this study, a light-activated allosteric modulator of A<sub>2A</sub>R was developed and successfully used to remotely induce sleep by selective light irradiation of the nucleus accumbens in mice.

Tsukuba, Japan—The nucleus accumbens plays a pivotal role in motivational behavior and sleep regulation, modulated by adenosine A<sub>2A</sub> receptors (A<sub>2A</sub>R). Hence, selective A<sub>2A</sub>R regulation within this brain region could control sleep and motivation. However, A<sub>2A</sub>Rs are distributed across various organs, including the heart, posing challenges for precise brain-specific modulation without genetic interventions.

A research team led by Professor Michael Lazarus and Associate Professor Tsuyoshi Saitoh (TRiSTAR Fellow) from the Institute of Medicine and the International Institute for Integrative Sleep Medicine (WPI-IIIS) at the University of Tsukuba delved into optochemistry. They aimed to develop a novel light-sensitive drug that enhances extracellular adenosine activity. By administering this drug to mice and selectively irradiating the nucleus accumbens with light, they succeeded in inducing sleep artificially without genetic modification for the first time.

Conventional photosensitive drugs have faced hurdles in mammals and other living organisms due to problems such as phototoxicity caused by ultraviolet light, blood-brain barrier permeability, and photoreaction efficiency. The newly developed photosensitive drug overcomes these issues, showcasing optochemistry's potential in developing drugs targeting A<sub>2A</sub>R in the brain and regulating brain function by targeting other central drug receptors.

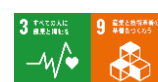
### Correspondence

Professor Michael Lazarus

Associate Professor Tsuyoshi Saitoh

International Institute for Integrative Sleep Medicine (WPI-IIIS) / Institute of Medicine, University of Tsukuba

URL: <https://iis-lazarus-oishi-lab.org/>



### Funding

This research was conducted as part of a research project funded by the World Premier International Research Center Initiative (WPI), Japan Science and Technology Agency CREST Grant (JPMJCR1655), Grants-in-Aid for Scientific Research (JP21H02802, JP23H04148), and AMED (JP21zf0127005).

### Article

“Optochemical control of slow-wave sleep in the nucleus accumbens of male mice by a photoactivatable allosteric modulator of adenosine  $A_{2A}$  receptors.” *Nature Communications*, April 30, 2024.

DOI: 10.1038/s41467-024-47964-4

### Keywords

Primary keyword: Sleep

Secondary keywords: Nucleus accumbens, Neuromodulators, Neural networks, Astrocytes, Photochemical reactions, Pharmacogenetics, Molecular neuropharmacology, Mouse models