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dr. christiane menzfeld

phone: +49 89 8578-2824
menzfeld@biochem.mpg.de
www.biochem.mpg.de/news
@MPI_Biochem

Sleep and synaptic rhythms

Chronobiologists show in two articles in the journal *Science* how critical the sleep-wake cycle is for protein and phosphorylation dynamics in synapses to ultimately regulate its activity.

The internal clock controls virtually all physiological processes in the human body predicting daily recurring environmental changes such as day and night. How the circadian rhythm and sleep influences molecular mechanisms at the cellular level in the brain is not yet fully understood. Professor Maria Robles, head of a research group at the Institute of Medical Psychology at LMU Munich, shows together with scientists from the Max Planck Institute (MPI) of Biochemistry, in two recent articles published in the journal *Science* how sleep and wake cycles, rather than the circadian clock, drive cycles of protein abundance as well as phosphorylation in synaptic proteins to orchestrate dynamics of synaptic activity in the brain.

The chronobiologist Maria Robles together with Matthias Mann and Jürgen Cox from the MPI of Biochemistry, used mass spectrometry-based quantitative proteomics to profile daily dynamics of protein and phosphorylation in in vivo isolated synapses from mouse forebrain. Phosphorylation means that phosphate molecules bind to proteins and change their structure slightly. The phosphate molecule thereby functions like a protein switch, capable of changing the protein activity and function.

For the studies in *Science*, the team investigated how synaptic proteome and phosphoproteome are dynamically shaped across the day and how it is affected by sleep deprivation. In one study the group shows that in a normal day, one fourth of the 8,000 phosphorylations in many critical synaptic proteins oscillates with two main peaks: one when the mice wake up and a second one just before they fall asleep. "This suggests that synaptic phosphorylation plays a key role in the regulation of synaptic function in particular at the sleep-wake-sleep transitions," says Maria Robles. This characteristic phosphorylation pattern seems to reflect buildup and dissipation of sleep and wake

pressure since sleep deprivation almost completely abolished synaptic phosphorylation rhythms. "Our study shows that key synaptic processes, from house-keeping to plasticity are temporally regulated trough phosphorylation, in response to both sleep and wake pressure," says Maria Robles, who worked as a postdoctoral fellow for Matthias Mann.

In the second study published in the same issue of *Science* the same group, in collaboration with a group from the University of Zürich (Steve Brown), has showed that synaptic protein abundance is also rhythmically shaped by sleep-wake cycles. In particular, they demonstrated that synaptic activity triggers the cycling production of proteins from messenger molecules that rhythmically accumulate at the synapses across the day. While protein production completely depends on wake-sleep cycles, messenger molecules travel and accumulate in the synapses predominantly in response to circadian mechanisms.

Original publications:

- F. Brüning, SB Noya, T. Bange, S. Koutsouli, JD Rudolph, S. Tyagarajan, J. Cox, M. Mann, SA Brown, MS Robles: Sleep-wake cycles drive daily dynamics of synaptic phosphorylation.
- SB. Noya, D. Colameo, F. Brüning, A. Spinnler, D. Mircsof, L. Opitz, M. Mann, S. K. Tyagarajan, MS Robles, SA Brow: The forebrain synaptic transcriptome is organized by clocks but its proteome is driven by sleep

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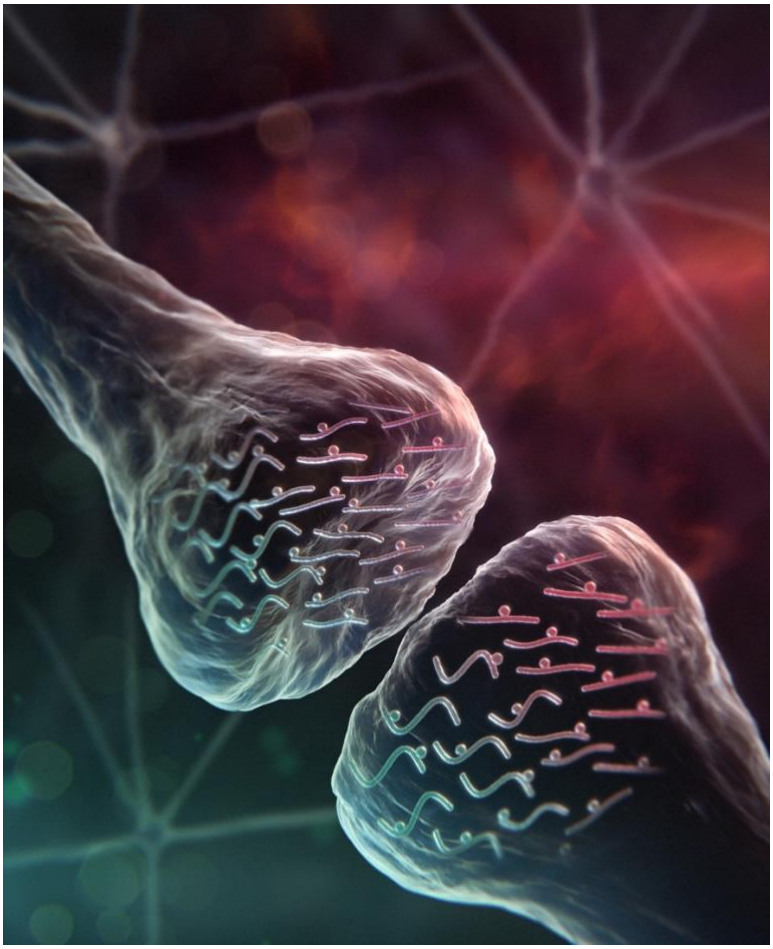
About the Max Planck Institute of Biochemistry

The Max Planck Institute of Biochemistry (MPIB) belongs to the Max Planck Society, an independent, non-profit research organization dedicated to top level basic research. As one of the largest Institutes of the Max Planck Society, 850 employees from 45 nations work here in the field of life sciences. In currently eight departments and about 25 research groups, the scientists contribute to the newest findings in the areas of biochemistry, cell biology, structural biology, biophysics and molecular science. The MPIB in Munich-Martinsried is part of the local life-science-campus where two Max Planck Institutes, a Helmholtz Center, the Gene-Center, several bio-medical faculties of two Munich universities and several biotech-companies are located in close proximity. http://www.biochem.mpg.de



Caption: At synapses, signals are transmitted from one nerve cell to the other. The proteins in the synapses influence the signal transduction.
Illustration: Max Iglesias

Contact:

Prof. Dr. Matthias Mann
Proteomics and Signal Transduction
Max Planck Institute of Biochemistry
Am Klopferspitz 18
82152 Martinsried
Germany

E-Mail: mmann@biochem.mpg.de
https://www.biochem.mpg.de/mann
Twitter: @labs_mann

Dr. Christiane Menzfeld
Public Relations
Max Planck Institute of Biochemistry
Am Klopferspitz 18
82152 Martinsried
Germany

Phone: +49 89 8578-2824
E-Mail: pr@biochem.mpg.de
www.biochem.mpg.de