Ras protein regulates circadian rhythm

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Biochemists at the Ruhr-Universität Bochum have gained new insights into the generation and maintenance of circadian rhythms. They demonstrated that the Ras protein is important for setting the phase of such a circadian clock, as its activity determines the period length of the rhythm. Ras is also contributing to induce phase-shifts in circadian rhythms in response to external time cues such as light. The team headed by Prof Dr Rolf Heumann published their results in the magazine *Molecular Neurobiology*.

Ras activity varies throughout the day

The circadian clock "ticks" in every cell of the body; a central master clock, however, is located in the brain, more specifically in the Nucleus suprachiasmaticus of the hypothalamus, which is old in genealogical terms. Its activity determines the cycle's period length, which is close to but not exactly 24 hours; it has to be continuously adjusted by external signals such as light, motor activity or food intake to an exact 24-hour rhythm. Such regulation is the result of many proteins acting and interacting in various signal cascades. A central switch for such signal cascades is the Ras protein, which is present either in its active or in its inactive form. The group from Bochum demonstrated in mice that Ras activity in the Nucleus suprachiasmaticus is high during the day and low during the night. Moreover, Ras activity was increased after brief exposure to light during the night.

Artificially increased Ras activity alters the circadian

rhythm

In collaboration with a Frankfurt-based team, headed by Prof. Dr. Jörg Stehle, the researchers from Bochum additionally studied the phenomenon in genetically modified mice, whose Ras activity is increased exclusively in neurons of the brain. They found that the activity in the Nucleus suprachiasmaticus oscillated with a significant shorter period than 24 hours - additional evidence for the relevance of Ras for the circadian rhythm.

Interplay with GSK3ß enzyme

The activity of the Ras protein is linked with the activity of an enzyme in the glycogen metabolism, namely GSK3ß. Via Ras, that enzyme is also involved in the regulation of circadian clock mechanisms. "Our findings are relevant in a larger context," says Rolf Heumann. "Other studies have shown that a dysregulation of the GSK3ß enzyme leads to major disturbances in circadian rhythms, and is linked to the symptoms of bipolar disorder."

More information: T. Serchov, A. Jilg, C.T. Wolf, I. Radtke, J.H. Stehle, R. Heumann (2015): Ras activity oscillates in the mouse suprachiasmatic nucleus and modulates circadian clock dynamics, Molecular Neurobiology, DOI: 10.1007/s12035-015-9135-0

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