SLEEP REGULATION

ppERK, sleep & fly

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Sleep is still a mysterious process. Its functions and regulatory mechanisms are unclear, but the fruit fly has emerged as a promising model system for uncovering its molecular underpinnings. Foltenyi *et al*. now show that a well-characterized pathway that involves epidermal growth factor receptor (EGFR) signalling regulates sleep in *Drosophila*.

The EGFR signalling pathway is similar in mammals and *Drosophila*. The transforming growth factor-α (TGF-α) homologues Spitz, Gurken and Keren (in *Drosophila*) can be processed by the transmembrane protein Star and the protease Rhomboid (Rho) and bind to EGFR, leading to activation of extracellular signal-regulated kinase (ERK).

The authors found that temporarily increasing the expression of *star* and *rho* in fruit flies caused an increase in their sleep time, followed by a compensatory decrease. Rho and Star act upstream of EGFR and, thus, expressing a dominant-negative form of the receptor abolished their effects on sleep.

The authors used RNA interference (RNAi) to generate flies in which Rho activity was reduced (rho^{DN} flies), first targetting the RNAi to all neurons and then to a restricted set of cells with the neural drivers c767, 50Y and c687. They found that this dramatically reduced total sleep levels, with a higher number but shorter duration of sleep bouts, indicating that flies with low Rho levels still required sleep but could not maintain it. The authors next induced expression of secreted Spitz in the same restriced set of neurons. This increased sleep time by 1 hour, further confirming that cells that are driven by c767, 50Y and c687 are involved in sleep regulation.

On the molecular level, the authors measured ERK activation in flies that overexpressed both *rho* and *star*, and found that high levels of phosphorylated ERK correlated with an increase in sleep time courses. No ERK hyperphosphorylation occurred in flies that co-expressed *rho* and *star* with a dominant-negative form of EGFR, confirming that ERK activation occurs downstream of EGFR activation. The authors further found that the high level of phosphorylated ERK that resulted

from *rho* and *star* activation clustered to the tritocerebrum in the fly brain. The neural drivers c767, 50Y and c687 were localized within the pars intercerebralis, which projects to the tritocerebrum. The pars intercerebralis might be the fly equivalent of the mammalian hypothalamus, a region of the brain that is known to regulate arousal.

This study shows that the EGFR–ERK pathway regulates the maintenance of sleep in *Drosophila*. This signalling pathway is common to mammals, suggesting that it might also have a role in sleep regulation in other species.

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ORIGINAL RESEARCH PAPER Foltenyi, K., Greenspan, R. J. & Newport, J. W. Activation of EGFR and ERK by rhomboid signaling regulates the consolidation and maintenance of sleep in *Drosophila*. *Nature Neurosci.* 12 Aug 2007 (doi:10.1038/nn1957)