SLEEP

sleepless pressure

Sleep is regulated in two opposing ways: by the circadian clock and by the homeostatic sleep drive. The molecular underpinnings of the homeostatic mechanism are poorly understood. Koh *et al.* have now identified sleepless (SSS), a protein that is required for homeostatic sleep pressure in *Drosophila melanogaster*.

In order to identify the molecular factors that drive animals to sleep, the authors carried out a genetic screen to find *D. melanogaster* mutants that exhibit reduced daily sleep. The mutant with the lowest amount of daily sleep was named *sleepless* (*sss*), as sleep was reduced to just 15% of normal levels. In these mutants, the *sss* gene carried a P-element insertion (sss^{P1}) in the coding region that resulted in the loss of SSS protein. Another insertion (sss^{P2}) in the 3′ untranslated region of the same gene resulted in a moderate reduction of SSS protein levels and in only a minimal reduction in sleep amount. Furthermore, sss^{P2}/sss^{P1} transheterozygous mutants exhibited ~30% of normal daily sleep amount and showed greatly reduced levels of SSS protein. These findings suggest that the amount of sleep directly correlates with SSS protein levels. This hypothesis is further corroborated by the fact that sleep duration in sss^{P1} mutants was restored to wild-type levels when the P-element insertion was excised or when wild-type *sss* was reintroduced transgenically.

Further characterization of SSS showed that it is a brain-enriched, glycosylphosphatidylinositol (GPI)-anchored cell-surface protein, the levels of which do not change throughout the circadian cycle. The GPI anchor could be cleaved by phosphatidylinositol-specific phospholipase C (PLC) to release SSS from the cell surface. Other GPI-anchored proteins function as ligands or co-receptors and can also act as diffusible signals when cleaved by PLC.

Next, the authors analysed the contribution of SSS to sleep homeostasis. Whereas control flies showed substantial rebound sleep after deprivation, sss^{P1}/sss^{P2} flies and sss^{P2} flies showed little or no rebound, providing evidence that SSS has a role in sleep homeostasis.

Interestingly, a previously described gene called quiver (*qvr*) has been mapped close to the *sss* gene locus. *qvr* mutants were shown to have severely reduced Shaker (SH)-dependent K^+ currents. The authors showed that *qvr* is in fact an allele of *sss*, and that SH protein levels are substantially reduced in sss^{P1} flies, indicating that SSS is an important regulator of the SH-dependent K^+ channel.

Together these findings indicate that SSS is an important regulator of homeostatic sleep. The authors propose that SSS might link homeostatic sleep drive to neuronal excitability by regulating the amount and activity of SH-dependent K^+ channels. Although no *sss* homologue has been identified in vertebrates, functional homologues might be found in the future.

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