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RESEARCH HIGHLIGHT

Sandman is a Sleep Switch in *Drosophila*

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Sleep is a universal process with vital functions. Animals deprived of sleep for a long period of time will die. Despite its crucial functions, fundamental questions about sleep remain unexplored. For instance, why do animals sleep since it disconnects animals from the external world and exposes them to danger (we really do not know!)? What is the switch between sleep and waking, if there is one (we may be beginning to understand this!)?

It has been found that sleep is controlled by two systems: the circadian clock and sleep homeostasis. The former determines the right time to go to sleep by synchronizing the internal circadian clock with the external world. Substantial progress has been made on the genetic and neuronal control of the circadian clock in the fruit fly *Drosophila melanogaster* [1], which was later shown to be similar in mammalian systems [2]. The latter, sleep homeostasis, measures internal "sleep pressure" (again, we do not know exactly what sleep pressure is!) and determines how much time animals spend asleep. Thus, studying the mechanism underlying sleep homeostasis is a key step in understanding sleep.

To understand sleep homeostasis, it is necessary to discover the key neurons that turn sleep on and off, and further determine the molecular regulators inside these neurons. Like the discovery of circadian clock genes and the neuronal circuitry in *Drosophila*, much progress has been made on the control of sleep homeostasis in *Drosophila* in recent years.

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First, neurons that promote or inhibit sleep have been identified in *Drosophila*. Notably, the artificial activation of dopamine (DA)-producing cells promotes wakefulness [3, 4], while activating a cluster of neurons innervating the dorsal fan-shaped body (dFB) of the central complex induces sleep [5]. In particular, two populations of DA neurons termed PPL1 and PPM3 project to the dFB neurons [3, 4]. These results suggest that DA released from the PPL1 and PPM3 neurons suppresses sleep by inhibiting the sleep-promoting dFB neurons. Thus, the dFB neurons could be a sleep-controlling center in the fly brain.

Second, electrophysiological evidence has suggested that the activity of dFB neurons represents sleep states. As noted above, the artificial activation of dFB neurons induces sleep [5]. Thus the dFB neurons would be more active during sleep, and less active during wakefulness. Donlea *et al.* recorded from dFB neurons and found that their excitability increases after deprivation of overnight sleep, and returns to baseline after rest [6]. However, how these neurons are activated to induce sleep and silenced to promote wakefulness remain the most challenging questions in understanding sleep homeostasis.

In a recent paper published in *Nature*, Pimental *et al.* combined optogenetics and electrophysiology in behaving *Drosophila*, and identified Sandman as a key protein to switch sleep off [7]. To record activity from dFB neurons in behaving flies, they tethered individual flies and placed them on an air-supported trackball, the rotation of which reflected their walking activity. Although it is hard to judge whether an individual fly is asleep when it does not walk on the trackball, during which times the recorded dFB neurons are persistently spiking, it is fair to say that the fly is awake when it starts walking on the trackball after at least 5 min of rest. Pimental *et al.* used optogenetics to remotely activate all DA neurons, including the PPL1 and PPM3

neurons that act upstream of dFB neurons, and found that the dFB neurons stop firing immediately after optical stimulation, and the flies become active (awaken). They also injected DA directly onto the dendritic region of dFB neurons and found a phenotype similar to activating all DA neurons. Furthermore, when the DA receptor Dop1R2 in dFB neurons was knocked down using RNAi, these neurons failed to respond to DA. Thus, DA released from active neurons functions *via* Dop1R2 to inhibit the dFB neurons and promote wakefulness.

Pimental *et al.* also found that after the activity of dFB neurons was inhibited by DA application or optical stimulation of DA neurons, they remained inactive for minutes without a further supply of DA, indicating a sustained effect of DA on promoting the awake state. They further discovered, by examining the electric properties of action potentials, that K^+ conductance mediates the bulk of the dopaminergic inhibition of dFB neurons. By knocking down selected genes encoding K^+ channels in dFB neurons, they identified several that promote or impair sleep, including the previously identified *shaker* gene that encodes the voltage-gated A-type K_v channel and promotes sleep [8], as well as the novel gene CG8713 that encodes the two-pore-domain K^+ (K_{2P}) channel, which the authors termed Sandman (a mythical character in European folktales who brings sleep and pleasant dreams). The electrical properties of active dFB neurons were unaffected by knocking down Sandman transcripts; however, these neurons continued to fire action potentials after DA stimulation. That is to say, DA was no longer able to wake the animal up, as it failed to inhibit dFB neurons lacking Sandman. Together with their findings and the known properties of K_{2P} channels, Pimental *et al.* proposed that Sandman is located in the cytoplasm when dFB neurons are active (sleep switch on), but transported to the plasma membrane to execute its function when DA switches the neurons off (sleep switch off). Thus, Sandman serves as a switch to turn off sleep by regulating the excitability of sleep-controlling dFB neurons. It is possible that equivalent molecular switches that reversibly turn sleep on might exist and await future exploration.

Sandman has orthologs in mammals, including humans. Whether Sandman works in a conserved way to regulate sleep is still unknown. But if it does, it will be an invaluable target for drug discovery for the treatment of insomnia.

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