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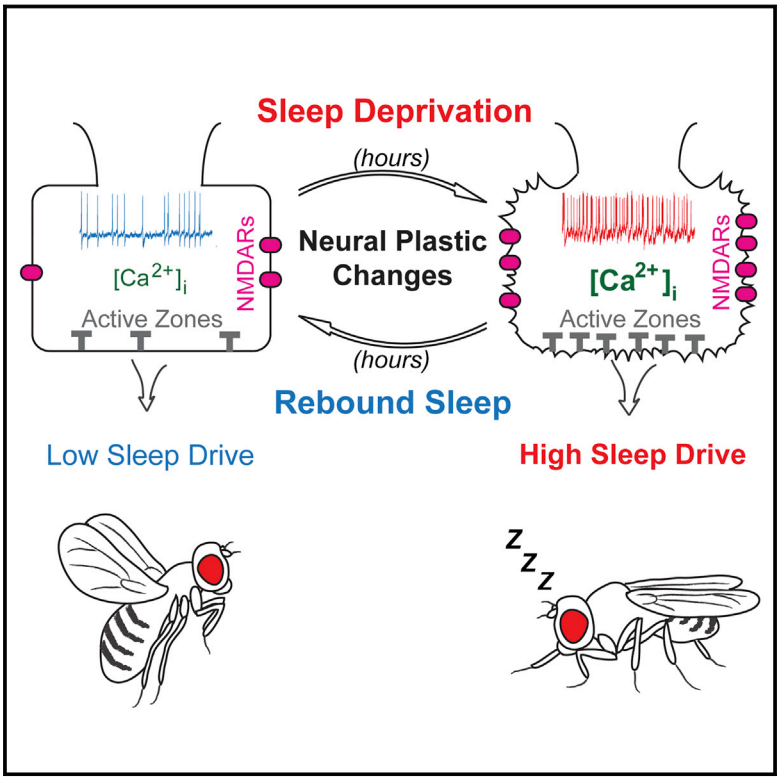
Sleep Drive Is Encoded by Neural Plastic Changes in a Dedicated Circuit

Graphical Abstract



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In Brief

Synaptic plasticity within a dedicated neural circuit encodes sleep pressure in *Drosophila* and provides a mechanistic explanation for the generation and persistence of sleep drive.

Highlights

- A subset of R2 EB neurons is capable of generating sleep drive in *Drosophila*
- Ca^{2+} levels and measures of synaptic strength in R2 cells correlate with sleep need
- R2 neuron translational profiling reveals increased NMDA receptors with sleep loss
- Manipulating synaptic strength of R2 neurons directly impacts homeostatic sleep drive

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Sleep Drive Is Encoded by Neural Plastic Changes in a Dedicated Circuit

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SUMMARY

Prolonged wakefulness leads to an increased pressure for sleep, but how this homeostatic drive is generated and subsequently persists is unclear. Here, from a neural circuit screen in *Drosophila*, we identify a subset of ellipsoid body (EB) neurons whose activation generates sleep drive. Patch-clamp analysis indicates these EB neurons are highly sensitive to sleep loss, switching from spiking to burst-firing modes. Functional imaging and translational profiling experiments reveal that elevated sleep need triggers reversible increases in cytosolic Ca^{2+} levels, NMDA receptor expression, and structural markers of synaptic strength, suggesting these EB neurons undergo "sleep-need"-dependent plasticity. Strikingly, the synaptic plasticity of these EB neurons is both necessary and sufficient for generating sleep drive, indicating that sleep pressure is encoded by plastic changes within this circuit. These studies define an integrator circuit for sleep homeostasis and provide a mechanism explaining the generation and persistence of sleep drive.

INTRODUCTION

The concept of homeostasis for maintaining stability of an animal's "internal milieu" was first articulated more than 150 years ago (Cannon, 1929). These principles are also relevant for motivated behaviors that are regulated by homeostatic drive (Berridge, 2004). Sleep is an archetypal example of such a behavior—prolonged wakefulness increases sleep drive (sleep pressure), resulting in an increase in sleep amount and/or depth ("sleep rebound") (Borbély, 1982). However, despite intense scrutiny for more than a century, the mechanisms underlying this process and the nature of sleep drive itself remain unclear. In addition, homeostatic regulation of motivated behaviors, such as feeding or sleeping, typically occurs over a long period (Berridge, 2004; Borbély, 1982); substantial accumulation of sleep drive in many animals takes hours of wakefulness and is often maintained for hours even after sleep is initiated (Daan et al., 1984; Huber et al., 2000, 2004). Therefore, unraveling the processes encoding sleep drive requires an understanding of both how sleep drive is generated and how it persists.

Most work on sleep drive has centered on extracellular sleep regulatory substances (SRSs), such as adenosine, whose levels rise with prolonged wakefulness in specific regions of the brain ("somnogen model") (Brown et al., 2012). These SRSs have traditionally been proposed to act on dedicated circuits that directly promote sleep or wakefulness in mammals, such as the ventrolateral preoptic nucleus (VLPO), median preoptic nucleus (MnPO), or specific acetylcholinergic nuclei (Methippara et al., 2005; Porkka-Heiskanen et al., 1997). In this model, sleep drive is generated by the accumulation of these SRSs, or "somnogens," in the extracellular space (Brown et al., 2012). However, the half-lives of these SRSs are typically much shorter (minutes) (Jonzon and Fredholm, 1985; Pettipher et al., 2007) than the time course for dissipating sleep pressure (hours), raising the possibility that, rather than directly encoding sleep pressure, these SRSs act as effectors of sleep drive to promote sleep (Benington and Heller, 1995).

From an engineering perspective, homeostatic systems require three components: (1) a sensor that periodically samples the state variable, (2) an integrator that processes this information to determine homeostatic drive, and (3) an effector that responds to this drive by directly manipulating the state variables (Enderle and Bronzino, 2012). Thus, general design principles predict that, for sleep homeostasis, central circuits should exist that both encode the amount of sleep pressure and play a crucial role in mediating the perdurance of such sleep drive. However, such circuits have not been previously found.

Here, from a large-scale forward screen of neuronal driver lines in *Drosophila*, we identify a neural circuit capable of generating sleep drive. Remarkably, activation of this circuit induces sleep pressure and persistent sleep behavior, even in fully rested animals. Conversely, neuronal silencing experiments reveal a specific requirement for this circuit in sleep homeostasis. Patch-clamp analysis demonstrates that this circuit is highly sensitive to changes in sleep need. Importantly, we find that intracellular Ca^{2+} levels and the synaptic strength of this circuit not only tightly correlate with, but are also able to specifically manipulate, the level of homeostatic sleep drive. Finally, cell-specific translational profiling reveals significant upregulation of NMDA receptors in this circuit following sleep deprivation, and we show that this upregulation is a key mechanism mediating "sleep-need"-dependent plastic changes in this circuit