This Week in The Journal

Interactions Among Starburst Amacrine Cells Create Waves

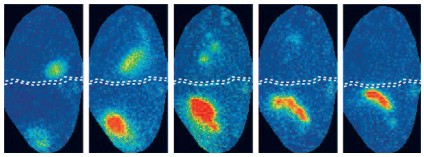
Hong-Ping Xu, Timothy J. Burbridge, Meijun Ye, Minggang Chen, Xinxin Ge, et al.

(see pages 3871–3886)

Many developing neural circuits are sculpted by spontaneous activity. Before the onset of vision, spontaneous waves of locally correlated activity propagate across the retina. In newborn mice, these retinal waves are initiated by spontaneous depolarization of starburst amacrine cells, which release acetylcholine onto retinal ganglion cells and other amacrine cells. Ganglion cells drive similar waves of activity in the superior colliculus and lateral geniculate nucleus, and this activity is required for proper segregation of inputs from the two eyes.

Computational models have suggested that acetylcholine-dependent retinal waves are generated by interactions among starburst amacrine cells, which then drive correlated bursting in nearby ganglion cells. To test this, Xu et al. deleted β2 nicotinic acetylcholine receptors, which are required for wave propagation, in starburst cells. The promoter they used to conditionally knock out the receptors becomes active gradually over the first postnatal week, leading to a gradual reduction of receptors between postnatal days 4 and 10. Waves of locally correlated ganglion cell spiking became progressively more truncated over this same period. Deletion of β2 receptors also reduced the segregation of inputs from the two eyes in the superior colliculus and lateral geniculate nucleus during the first postnatal week, underscoring the importance of cholinergic waves in this form of circuit refinement.

The results support the hypothesis that acetylcholine-dependent retinal waves occurring during the first postnatal week are generated by recurrent connections between starburst amacrine cells. They further suggest that the pattern of activity generated in starburst cells is transmitted to retinal ganglion cells and downstream visual centers to shape circuits, and they highlight the importance of cholinergic neurotransmission between starburst cells in generating these waves. Thus, the work advances our understanding of these so-called stage II waves. Elucidation of the mechanisms and functions of gap-junction-dependent stage I waves, which occur before birth, and of glutamatergic stage III waves, which occur in the second postnatal week, will be required to fully appreciate the role of spontaneous activity in shaping visual circuits.



Time-lapse images of retinal waves propagating across the axonal arbors of retinal ganglion cells that terminate in the right (above dashed lines) and left (below dashed lines) superior colliculus. See Xu et al. for details.

Glial Adenosine Kinase Influences Sleep Homeostasis

Theresa E. Bjorness, Nicholas Dale, Gabriel Mettlach, Alex Sonneborn, Bogachan Sahin, et al.

(see pages 3709–3721)

The longer we stay awake, the more our need for sleep grows. This increased need is paralleled by increases in the magnitude and duration of slow-wave activity when we finally sleep. Over the course of sleep, the sleep drive and the power of slow-wave activity gradually decrease.

Much evidence suggests that the homeostatic regulation of sleep drive depends on adenosine. Extracellular adenosine levels increase in the cortex and basal forebrain during prolonged wakefulness and decline during sleep; adenosine inhibits arousal-promoting cholinergic basal forebrain neurons; and adenosine receptor antagonists such as caffeine promote wakefulness. Learning how extracellular adenosine levels are modulated might therefore lead to a deeper understanding of sleep homeostasis and its disruption.

Increases in extracellular adenosine during wakefulness likely stem from a combination of elevated energy consumption associated with increased neural activity and synaptic and glial release of ATP, which is metabolized extracellularly to form adenosine. Extracellular adenosine is transported into cells, where it is metabolized to inosine by adenosine deaminase or phosphorylated to AMP by adenosine kinase. A role for adenosine deaminase in sleep regulation is suggested by the fact that an allelic variation that reduces deaminase activity is associated with increased duration and intensity of slow-wave sleep in humans. Adenosine kinase activity has also been suggested to influence sleep.

To further investigate the role of adenosine kinase in sleep regulation, Bjorness et al. generated transgenic mice in which glial expression of this enzyme was reduced by ~20%. This led to a significant increase in extracellular adenosine levels and an increase in slow-wave activity during both sleep and waking. Furthermore, mice with reduced glial expression of adenosine kinase showed a greater increase in slow-wave activity after sleep deprivation than controls. Finally, the time constant of the decay in slow-wave activity within a bout of sleep—which the authors demonstrated to be a reliable measure of sleep pressure—was much greater in adenosine-kinase-deficient mice than in controls.

These results indicate that adenosine kinase is an important regulator of extracellular adenosine levels and thus contributes to the homeostatic regulation of sleep. Moreover, they highlight the importance of glia in ensuring we get enough sleep.

This Week in The Journal is written by Teresa Esch, Ph.D.