This Week in The Journal

Sleep-Dependent Regulation of Glutamate Uptake

Chantalle Briggs, Michiru Hirasawa, Kazue Semba

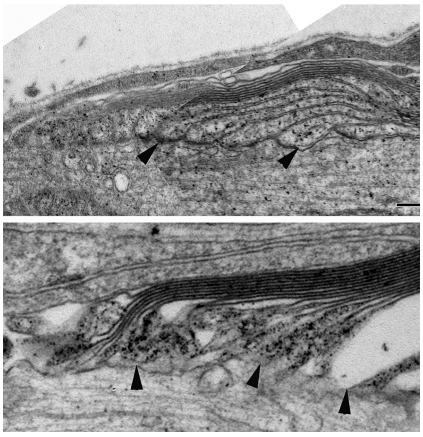
(see pages 2505–2518)

Astrocytes regulate neuronal activity in numerous ways. For example, astrocyte processes engulf synapses and take up excess extracellular glutamate, thus limiting its spillover to extrasynaptic sites where it can activate metabotropic glutamate receptors (mGluRs). Notably, astrocytic regulation of neurotransmission varies across the sleep–wake cycle. For example, astrocytes phagocytose large synapses after prolonged periods of wakefulness, possibly helping to prevent excessive potentiation (Bellesi et al. J Neurosci 37:5263).

Briggs et al. now report that regulation of neuronal activity by astrocytes also varies across cell types in the lateral hypothalamus. This area contains orexin-releasing neurons, which promote arousal and continued wakefulness, as well as neurons that release melanin-concentrating hormone (MCH), which are active primarily during REM sleep. Depriving rats of sleep for 6 h caused the levels of glutamate transporter 1 (GLT1)—a predominantly astrocytic protein that mediates glutamate uptake—to change in opposite directions around orexin and MCH neurons. Specifically, GLT1 expression adjacent to the somata of orexin neurons was lower in sleep-deprived than in resting rats, whereas GLT1 expression around MCH neurons was higher after sleep deprivation than at rest.

Differences in GLT1 expression were associated with changes in synaptic transmission that suggested modulation of mGluR activation. In orexin neurons, sleep deprivation increased the paired-pulse ratio (suggesting it reduced presynaptic release probability) at glutamatergic synapses, mimicking the effect of inhibiting GLT1; these effects were blocked by a group III mGluR antagonist. Although neither sleep deprivation nor GLT1 inhibition affected paired-pulse ratio in MCH neurons, the amplitude of slow EPSCs produced by stimulation trains was reduced in these neurons after sleep deprivation. Importantly, previous work has shown that these slow EPSCs are mediated by postsynaptic group I mGluRs.

These results suggest that glutamate uptake by astrocytes can vary with behavioral state and across neuronal populations. After prolonged wakefulness, GLT1 expression decreases around orexin neurons. This likely allows glutamate to accumulate and activate presynaptic mGluRs, thus reducing excitatory drive to these arousal-sustaining neurons and increasing the likelihood that the animal will fall asleep. At the same time, GLT1 expression increases around MCH neurons. This likely reduces glutamate accumulation, prevents activation of postsynaptic mGluRs, and thus prevents premature activation of MCH neurons while the animal is still awake. In this way, astrocytes may help ensure proper functioning of the sleep–wake cycle.



In normal nerves (top) the edges of each wrap of the myelin sheath adheres to the axon and forms paranode structures (between arrowheads). Knocking out *QKI* (bottom) disrupts these structures. See Panganiban, Barth, Darbelli, et al. for details.

Noise-Induced Changes in Auditory-Nerve Myelin

Clarisse H. Panganiban, Jeremy L. Barth, Lama Darbelli, Yazhi Xing, Jianning Zhang, et al.

(see pages 2551–2568)

Exposure to noise can cause hearing loss. Extremely loud noise kills auditory hair cells and thus permanently raises thresholds for sound detection. But even moderate noise that leaves hair cells intact can impair hearing by disrupting synapses between hair cells and spiral ganglion axons. Although such synaptic loss does not affect auditory thresholds, it degrades auditory discrimination in noisy environments. Noise exposure can also cause demyelination of auditory nerves, slowing conduction times and disrupting temporal coding, thus impairing sound localization and language comprehension.

To elucidate the effects of noise exposure on myelin, Panganiban, Barth, Darbelli, et al. exposed mice to 106 dB noise, which is loud enough to kill hair cells that respond to frequencies >45 kHz. Disruption of myelin—particularly at paranode structures adjacent to nodes of Ranvier—was seen immediately after noise exposure; disruption became more pronounced over the subsequent 14 d, and persisted for at least 30 d. Consistent with loss of myelin, conduction velocities were slowed. Macrophages were also present in the auditory nerve, likely clearing myelin debris. Furthermore, expression of >900 genes was altered in the auditory nerve within the first day of noise exposure. Many of these genes were related to immune responses, but numerous myelin-associated genes were also affected. Notable among these was *QKI*, which encodes an RNA-binding protein (Quaking) involved in myelin differentiation. Although only one of the three major alternatively spliced isoforms of *QKI* was significantly altered, expression of several QKI targets was affected.

To determine whether dysregulation of QKI might contribute to myelin abnormalities and conduction delays in auditory nerves, the authors knocked out *QKI* in adult glia. This lead to demyelination and disruption of paranode structures. As expected, the disruption of myelin was associated with delayed auditory brainstem responses, although auditory thresholds and amplitudes were not affected.

These results show that disruption of auditory-nerve myelin begins immediately after exposure to loud noise. Noise causes a large shift in myelin gene expression in the nerve, partly by changing the relative expression of *QK1* isoforms. Such changes might contribute to noise-induced hearing loss.

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