This Week in The Journal

Astrocytes Speed Action Potential Propagation

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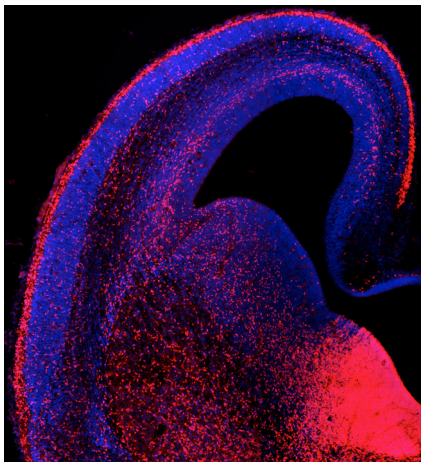
(see pages 11105–11117)

Glia affect neural circuits in numerous ways. Microglia strip synapses and clear debris after injury; oligodendrocytes form myelin, which regulates axon conduction velocity and limits sprouting; and astrocytes direct blood flow to active circuits, provide nutrients and growth factors, regulate extracellular ion concentrations, guide neurite growth, promote synaptogenesis, stabilize dendritic spines, and encapsulate synapses to limit the spread of neurotransmitters. Accumulating evidence suggests that astrocytes also influence axonal conduction, for example, by releasing glutamate and ATP along the axon and by regulating extracellular potassium levels at nodes of Ranvier (reviewed in Fields et al. 2015 Neuron 86: 374). Sobieski et al. add to this evidence by showing that action potential shape and propagation speed differ in isolated hippocampal neurons grown in contact with (+) or without (no-) astrocytes.

The first clue that astrocytes affected axonal propagation was the unusual shape of autaptic EPSCs evoked by current injection into no-astrocyte neurons. Not only were the time to peak greater and the peak amplitude lower in no-astrocyte neurons than in +astrocyte neurons, but a large-scale asynchrony involving multiple peaks was apparent in EPSCs of no-astrocyte neurons. Importantly, the timing of local peaks within EPSPs was largely invariant across trials, their amplitudes were much larger than quantal amplitudes, and they were insensitive to calcium chelators, suggesting they did not result from delayed release of single vesicles triggered by persistent calcium elevation in axonal terminals. Instead, the multiple peaks seemed to result from asynchronous arrival of action potentials at different terminals. Indeed, action potential propagation speed was significantly reduced in no-astrocyte neurons, which would likely cause release at distal terminals to be delayed relative to release more proximal to the soma. In addition, the spike width was greater in distal axons of no-astrocyte neurons than in +astrocyte neurons.

These data suggest that astrocytes regulate the rate of action potential propagation and thus the synchrony of release across synaptic terminals. Thus, astrocytes may have a profound impact on neuronal processes that rely on precise spike timing, such as dendritic integration and coincidence detection, spike-timing-dependent synaptic plasticity, and the binding of features represented in different brain regions through synchronous activity.



GABAergic neurons (red) generated in the MGE (bottom right) migrate tangentially to populate the developing cerebral cortex. See Skorput et al. for details.

Gestational Ethanol Exposure Increases Inhibition in mPFC

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(see pages 10977–10988)

Prenatal alcohol exposure alters brain development, leading to long-lasting physical, behavioral, and/or cognitive effects. The type and severity of these effects depends on the timing, duration, and magnitude of exposure, but impaired executive functions, including deficits in working memory, response inhibition, and cognitive flexibility (the ability to shift problem-solving strategies), are common even in people with the mildest forms of fetal alcohol spectrum disorder.

The medial prefrontal cortex (mPFC) is a key mediator of executive control, and behavioral flexibility requires intact functioning of GABAergic neurons in this brain area. Previous work (Cuzon et al. 2008 J Neurosci 28:1854) revealed that when pregnant mice consumed moderate levels of ethanol during the first two weeks of pregnancy, GABAergic neurons in embryos migrated more quickly from their site of origin in the medial ganglionic eminence (MGE) to the cortex, increasing the density of GABAergic neurons in cortex at embryonic day 14.5 (E14.5).

To further investigate the effects of prenatal ethanol exposure on the development of inhibitory circuitry, Skorput et al. used a binge-like ethanol exposure regimen restricted to the period of peak interneuron migration (E13.5–16.5). This treatment increased by ~35% the density of MGE-derived neurons in the mPFC, and the increase persisted into young adulthood. Inhibitory input to mPFC layer V pyramidal cells was also greater in mice exposed to ethanol *in utero*, and the ratio of inhibitory and excitatory inputs (I/E) was 3-fold greater in ethanol-exposed mice than in controls.

Mice exposed to ethanol *in utero* also showed impaired behavioral flexibility: Although they were as proficient as controls in learning the location of an escape hole in a circular maze (a hippocampus-dependent task), they were slower to find the hole when it was moved, largely because they continued to search in the original location. The extent to which this deficit resulted from the shift in I/E balance remains to be demonstrated, however.

The period of ethanol exposure used in this study is gestationally equivalent to the middle of the first trimester in humans. At this time, women may be unaware that they are pregnant. Therefore, the results reported here underscore the admonition that women who might be pregnant should limit alcohol consumption.

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