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Oligodendrocytes Changing the Rules: Action Potentials in Glia and Oligodendrocytes Controlling Action Potentials

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Abstract

Two long-standing rules in cellular neuroscience must now be amended with the publication of two studies on myelin-forming glia in the CNS: 1) Neurons can no longer be considered the only cells that fire electric impulses in the brain. 2) Synapses between neurons are not the only way electrical information is regulated as it propagates through neural circuits: oligodendrocytes can cause rapid activity-dependent changes in spike latency. A category of oligodendrocyte precursor cells (OPCs) has been identified that can fire action potentials, and their excitation is driven by synapses from axons. This finding has relevance to excitotoxicity in ischemia, but the normal function may be to regulate myelination according to functional activity in axons. A second study reveals that action potential propagation through CNS axons can be rapidly regulated by oligodendrocytes. Mature oligodendrocytes in the rat hippocampus are depolarized by theta burst stimulation of axons, and when the oligodendrocytes are depolarized by current injection in paired whole-cell recordings with CA1 pyramidal neurons, the latency of impulse conduction through the axons it ensheathes rapidly decreases. This unprecedented finding suggests a dynamic role for myelin in regulating impulse transmission through axons, promoting neural synchrony among the multiple axons under the domain of an individual oligodendrocyte.

Keywords

Myelin; Oligodendrocyte; Ischemia; Conduction velocity; Spike timing plasticity; DTI; Hippocampus; OPC

It has been known for some time that all major categories of glial cells, including astrocytes, Schwann cells, oligodendrocytes, and microglia, have many of the same ion channels as neurons (Verkhratsky and Steinhäuser 2000; Chittajallu and others 2004), but in contrast to neurons, glia do not generate action potentials. Injecting current into some types of glial cells under appropriate conditions in cell culture can induce action potentials (Sontheimer and Waxman 1992), but this was not believed to occur naturally in the brain. This physiology is reasonable, because no purpose for glial excitation is evident. Similarly, it has been known for some time that glia have many of the same neurotransmitter receptors used by neurons in synaptic communication (Patneau and others 1994). Sensitivity to neurotransmitters allows glia near the synaptic cleft to sense synaptic transmission and even modulate it (Fellin and others 2006; Bains and Oliet 2007), but why would myelinating glia associated with axons far removed from the synapse have these receptors? Both new papers report previously unseen features of cells in the oligodendrocyte lineage indicating that neurotransmitter receptors and

ion channels allow activity-dependent regulation of myelinating glia in the developing and adult brain.

Impulses Generated in White Matter Glia

Oligodendrocytes express a proteoglycan, NG2, at an immature stage termed the oligodendrocyte precursor cell (OPC) (Nishiyama and others 1996, 2002; Butt and others 1999). Later in development, OPCs mature into oligodendrocytes that form the myelin insulation on rapidly conducting axons. Curiously, NG2+ cells also persist in the adult CNS, where they compose up to 5% of brain cells. Intriguingly, NG2+ cells are the main population of cells that proliferate in the adult brain, making them of great interest in the context of regeneration and remyelination (Dawson and others 2003). Electrophysiological recordings and electron micrographs have shown that many of these cells are coupled to axons through synapses that utilize glutamate or GABA as neurotransmitters (Bergles and others 2000), but the significance of this neuron-glia synapse is unknown.

In a recently published article, patch clamp recordings by Káradóttir and colleagues (2008) performed in OPCs in white matter areas of the cerebellum of postnatal-day-7 rats revealed that half of the NG2+ cells fire action potentials (Fig. 1). As with classical action potential generation in neurons, these glial action potentials are mediated by transient inward sodium currents and voltage-gated outward potassium currents. Both classes of OPCs can proliferate, and no morphological differences distinguish the spiking OPCs from the nonspiking OPCs. Further experiments showed that the OPCs exhibiting sodium currents could generate action potentials spontaneously or in response to depolarization; moreover, these glial cells receive synaptic inputs.

This class of OPCs empowered with the ability to sense neurotransmitter and fire electric impulses, however, now faces the sword of Damocles imperiling the regal neuron: vulnerability to glutamate excitotoxicity. Under ischemic conditions that cause the release of glutamate from axons (Káradóttir and others 2005; Micu and others 2006), the OPCs expressing voltage-gated sodium channels and large glutamate currents are selectively killed (Káradóttir and others 2008).

Thus, OPCs are not a uniform class of cells. This raises questions of how these two classes differ in diseases of white matter and in its repair. Should these electrically excitable OPCs be the preferred cells in transplants to promote remyelination in multiple sclerosis or spinal cord injury? Additionally, some brain tumor cells presumed to derive from neurons, because they are electrically excitable, may instead derive from these electrically active OPCs (Káradóttir and others 2008).

Despite the important clinical relevance of this new finding, the ability to sense glutamate and respond by firing action potentials must serve an important function under natural conditions, rather than serving solely as a mechanism to kill the cells during ischemia. The authors speculate that, as in a muscle cell, the glial spike serves as a cell-wide signal in the OPC. Given the evidence that myelination can be regulated by ion channel activation (Demerens and others 1996) or electrical activity in axons (Stevens and others 1998; Stevens and Fields 2000; Stevens and others 2002, 2004; Ishibashi and others 2006), the authors suggest that this category of electrically excitable OPCs may sense axons that fire impulses and myelinate them preferentially. This could modulate brain development and plasticity in white matter tracts according to functional activity and experience (Fields 2005, 2008).

White Matter Glia Dynamically Regulate Conduction Velocity

The second study revealing new oligodendrocyte functions explores the consequences of action potentials in axons communicating with mature oligodendrocytes and the reciprocal effects on impulse propagation. Yamazaki and colleagues (2007) recorded electrophysiological responses from mature oligodendrocytes in the myelinated region of rat hippocampus, the alveus (Fig. 2). This enables measurement of action potential conduction velocity in axons of the pyramidal neurons. Exogenously applied glutamate elicited depolarizing responses through NMDA and non-NMDA receptors, and electrical stimulation at the border between the alveus and striatum evoked inward currents in the oligodendrocyte that were mediated by glutamate and potassium channels. Theta-burst stimulation of the hippocampus, which resembles *in vivo* activity and induces long-term potentiation of hippocampal synapses, depolarized the oligodendrocytes to a potential of -48 mV from a resting membrane potential of -75 mV. Because axons are known to release glutamate and potassium after firing bursts of action potentials (Kriegler and Chiu 1993; Kukley and others 2007; Ziskin and others 2007), the depolarizing response in oligodendrocytes to the axonal firing is not unexpected; indeed, they were observed in optic nerve glia (astrocytes) 40 years ago (Orkand and others 1966), but the significance, if any, of the depolarization in oligodendrocytes is obscure.

To explore the hypothesis that this activity-dependent axon-glial communication might have consequences for neuronal function, the investigators performed paired whole-cell recordings between oligodendrocytes in the alveus and pyramidal cells in CA1 while stimulating axons from the pyramidal cells distally in the alveus to elicit antidromic action potentials (Fig. 2). In a subset of these paired-cell recordings (4 of 27), the latency of the antidromically activated spikes decreased when the oligodendrocyte was depolarized to -30 to -20 mV (Fig. 3B). After the experiment, the oligodendrocytes and pyramidal cells filled with biocytin during the paired recording were examined histologically (Fig. 3A). In those experiments where the action potential latency had decreased after depolarizing the oligodendrocyte, the filled axon was observed to pass through a myelinated segment extending from the depolarized oligodendrocyte. In those cases where there was no decrease in action potential latency, the axons did not pass through the oligodendrocyte that had been depolarized. The authors speculate that the increase in conduction velocity may be caused by osmotic swelling of the myelin sheath secondary to transmembrane ion fluxes during depolarization.

These observations are based on a small number of cases, but they are unprecedented. If confirmed by further experiments and the mechanisms can be elucidated, the implications of modulating impulse propagation speed by rapid activity-dependent responses in myelin will not only change our current concept of myelin but also add a new dimension to information processing in the brain. Communication between neurons is primarily regulated by changes in synaptic efficacy, but in theory, information processing would also be regulated by changes in conduction velocity, which would affect spike arrival timing and synchrony (Fields 2005, 2008). Spike arrival timing can be critical in information coding (Gollisch and Markus 2008). Because an individual oligodendrocyte can myelinate 20 or more axons simultaneously, all the axons under the domain of the same glial cell would be influenced in a coordinated manner. The consequences of glial involvement in information processing, particularly in white matter, are yet to be explored experimentally and conceptually.

Conclusion

These two unexpected observations rewrite the pages of neuroscience and force a rethinking of myelin as static and relevant primarily in the context of disease. Myelinating glia are far more dynamic than assumed. They are responsive to electrical activity in the axons to which they are so closely associated, and they modulate axonal function on a much more rapid time

scale than had been imagined. New methods of imaging microstructure in white matter, such as diffusion tomographic imaging, are revealing plasticity in white matter that correlates not only with dysfunction but also with normal function (Fields 2008). Like all adjacent cells in the body, myelinating glia and axons communicate, and the dialog is not one-way. This class of OPCs and mature oligodendrocytes can, in these contexts at least, interact dynamically with electrical impulse transmission in neural circuits.

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Fig. 1. Oligodendrocyte precursor cells (OPCs) in white matter tracts of the rat cerebellum can fire spontaneous action potentials. *A*, OPCs are identified by double staining for NG2 (green) and the transcription factor OLIG1 (red). *B*, Spontaneous action potentials in OPC mediated by sodium and potassium currents. Reprinted from Káradóttir and others (2008), with permission.

Fig. 2. Schematic diagram of experiments by Yamazaki and others (2007) revealing that depolarization of oligodendrocytes can decrease the latency of action potentials in axons in the rat hippocampus. Theta burst stimulation of axons depolarized the oligodendrocytes by activating glutamate and potassium channels in the oligodendrocyte. Paired cell recordings between oligodendrocytes (R_{oligo}) and pyramidal neurons (R_{pyr}) were used to monitor and regulate voltage responses in oligodendrocytes. Action potentials were stimulated by antidromic stimulation (S) for measurements of action potential conduction velocity. Conduction velocity increased in axons myelinated by the oligodendrocyte that was depolarized.

Fig. 3. Depolarization of oligodendrocytes in the rat hippocampus can reduce action potential latency through the axons ensheathed by the cell. *A*, Axon (triangles) and oligodendrocyte filled with biocytin in paired whole-cell recordings. *B*, Depolarization of the oligodendrocyte reduced the spike latency in axons ensheathed by the oligodendrocyte within seconds, and the latency returned to baseline after restoring normal resting potential in the oligodendrocyte. Reprinted from Yamazaki and others (2008), with permission.