

PERSPECTIVES

A passive cable to excite oligodendrocyte precursor glia

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Not long ago, glial cells were thought to have a typical linear rectification of membrane current and lack action potentials, a defining feature of neurons. But these boundaries are blurring. Oligodendrocytic precursor cells (OPCs), identified by expression of the proteoglycan NG2, appear during early postnatal life and maintain the capacity in adulthood to proliferate into oligodendrocytes producing myelin sheaths and performing myelin repair. OPCs appear to be a surprisingly excitable phenotype. They are morphologically characterized by radially projecting long and thin branches containing AMPA, NMDA and GABAergic receptors and receive direct synaptic inputs from neighbouring neurons (Lin & Bergles, 2004). Some NG2⁺ OPC classes even produce fast action potentials reminiscent of neurons (Kárádóttir *et al.* 2008). These findings raise the intriguing possibility that OPCs, similarly to neurons, perform intricate electrical computations. However, how synaptic currents spread along the OPC branches is not understood. In this issue of *The Journal of Physiology*, Chan *et al.* (2013) make a substantial contribution towards answering these emerging issues.

Passive-cable theory, developed in the late 1950s by Rall and colleagues, provides a mathematical framework to describe the current flow and electrical characteristics of dendrites and axons by reducing these into equivalent cylinder models (Rall *et al.* 1992). The ability of a synapse, or its electrical voltage transient, to influence output can be analytically solved if one knows three basic parameters: the specific membrane resistance (R_m), intracellular core resistance (R_i) and membrane capacitance (C_m). These cable parameters, together with the specific cell geometry, determine the time

course, spread and efficacy of current flow in neuronal dendrites.

In a technical *tour de force*, Chan *et al.* used dual whole-cell patch-clamp recordings from rat hippocampal NG2⁺ OPCs combined with two-photon microscopy to create detailed three-dimensional anatomical reconstructions. Numerical compartmental models constrained by the morphology of the same cell were used to fit the recorded voltage transients and extract R_m , R_i and C_m (Rall *et al.* 1992). While R_i and C_m were within the range of values typically found in neurons, the authors show that OPCs have a unique low R_m . Remarkably, by placing the second recording electrode directly at one of the OPC processes, the specific membrane resistance was observed to distribute uniformly in the soma and branches.

The development of an OPC passive-cable model creates important new insights. Firstly, information can be obtained from subcellular regions from which it is otherwise impossible to make recordings. For example, in the tip of the OPC branches simulated EPSPs were predicted to be larger in amplitude compared to the soma. Such non-uniformity in EPSP amplitudes can be explained by the time course of synaptic current, which in small and electrically isolated compartments can be fast enough to be independent of R_m , charging mainly the local input capacitance and intracellular resistance. Secondly, by virtue of a low R_m the EPSPs strongly attenuate in peak amplitude when propagating towards the soma, making the branches act as a linear filter. Thirdly, the EPSP amplitude and time course at the soma were found to be independent of synapse location, a phenomenon called ‘passive normalization’. The emerging picture of the OPC suggests a passive electrotonic structure that is optimized for highly compartmentalized input processing, a hypothesis that needs to be tested by, for example, imaging frequency-dependent Ca²⁺ responses in OPC processes.

A low R_m reflects a high resting membrane conductance. Indeed, the authors identified that R_m is determined by inward-rectifying potassium (Kir) channels. Kir channels are known to be major players in glial

physiology given their role in setting the resting membrane potential and regulation of extracellular uptake of K⁺. This is particularly interesting in light of the severe myelination deficits in Kir4.1 knockout mice (Neusch *et al.* 2001).

Major new questions are arising from this study. Neurons use their cell-specific dendritic geometries and arrangement of biophysical membrane properties to enrich the computational capacity in the form of temporal coding with axonal action potential output. But what is the output of oligodendrocyte precursor glia? Is a sub-millisecond precise EPSP integration time window required and is there a temporal code to activate OPC proliferation and differentiation? This remains very speculative. NG2⁺ OPCs are efficiently recruited towards areas of myelin injury by means of the formation of new synaptic inputs (Etxeberria *et al.* 2010). Based on the passive-cable model, γ frequencies would be optimal for temporal summation in OPC branches. However, *in vivo* temporal summation will be much more complex than the passive scenario as OPCs also express voltage-gated sodium and calcium channels adding non-linearity to the membrane depolarization (Kárádóttir *et al.* 2008; Haberlandt *et al.* 2011). Future work needs to furnish the passive-cable models with active conductances to test whether OPC branches are capable of performing non-linear operations.

In summary, the study of Chan *et al.* provides the basic tools for computational analyses of OPC functions. Compartmental models help interpret electrophysiological data but also make it possible to produce testable quantitative predictions, undoubtedly inspiring new electrophysiological and imaging studies to gain further insight into the rules of synaptic integration in oligodendrocyte precursors. Passively exciting new avenues in the study of glia physiology are therefore lying ahead.

References

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