Effects of cellular adaptations to partial demyelination on spike patterns in a model axon.

Jay S. Coggan[1] and Terrence J. Sejnowski [1]
The Salk Institute for Biological Studies, La Jolla CA, USA

In a computational model, axons undergoing demyelination can produce a wide variety of spike patterns ranging from conduction failure to high-frequency bursting. We have simulated cellular adaptations to partial demyelination to understand what an axon might gain from adaptations to changes in excitability. Observed clinical phenomena in multiple sclerosis include an increase in axon diameter and the aggregation of mitochondria during demyelination. We, therefore, examined the effect of axon diameter swelling and increased activity of Na-K pumps on axonal excitability. Increasing the diameter of a partially demyelinated axon by 2-fold (as has been observed in human cases) had the effect of increasing the “safety factor” for successfully conducting a single spike across a demyelinated patch by 37% uniformly across a wide range of ion channel densities. At the other end of pathological spike behavior range, the un-evoked burst-pattern threshold was unaffected by the girth doubling at physiologically relevant densities of ion channels. Only at unusually high densities was a lower burst-threshold observed (-43%). But another measure of burst activity was altered by cable swelling. In the control demyelinated axon the frequency of bursting followed an oscillating pattern that was dependent on membrane current density. This sinusoidal frequency-density relationship was nearly flattened, or damped, by axon swelling. We addressed mitochondrial accumulation by assuming this cellular adaptation would impact Na-K pump activity. We discovered that increasing the Na-K pump activity only in the demyelinated areas caused early termination of the un-evoked bursting behavior. Our results suggest new interpretations of previous clinical and electrophysiological observations related to axonal intrinsic excitability in demyelination diseases. NIMH R01MH079076 and HHMI.