Conductance Imbalances Link Diverse Symptoms of Demyelination Diseases

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White matter in both the central and peripheral nervous systems is susceptible to damage that results in the disruption of the oligodendrocyte or Schwann cell associated myelin insulation. Demyelination upsets the normal saltatory propagation of action potentials (AP) resulting in slowed, blocked, desynchronized or paradoxically excessive neuronal activity in any modality and producing a broad spectrum of symptoms. The diversity and timing of demyelination symptoms are poorly understood, often intermittent and uncorrelated with disease progress. We have examined the effects of demyelination and related ionic conductance alterations on axonal intrinsic excitability using a Hodgkin-Huxley (HH) based compartmental model of a mammalian myelinated fast-spiking axon and a reduced Morris-Lecar (ML) dynamical analysis. Our model provides a simple explanation for a breadth of symptoms and reveals how the ratio of sodium to leak conductance, a (gNa/gL), acts as a four-way-switch that governs complex intrinsic excitability patterns in partially demyelinated axons including: spike-failure, single spikes, afterdischarge, or spontaneous behavior. Modeling results demonstrate that afterdischarge requires a slow positive feedback mechanism that renders the system bistable with two coexisting attractor states; one corresponding to quiescence and the other to repetitive spiking. The bistability required for afterdischarge can result from smaller changes in excitability than those required to destabilize the system so that it spikes spontaneously. A neuron prone to afterdischarge may function normally unless a trigger switches the system to its “pathological” attractor state. Although the underlying pathology may develop slowly, the manifestation of the pathology develops abruptly, and could explain the broad variety of paroxysmal symptoms (pain, paresthesias, spasms, etc) experienced by MS patients. Support HHMI, NIH (TJS)