



## Molecular players shown to affect nerve fibers in multiple sclerosis

Until recently, researchers knew very little about the neural molecules associated with secondary progressive multiple sclerosis (MS), a nerve-degenerating autoimmune disease that afflicts almost 3 million people worldwide. Scientists had typically studied the disease in mouse models, but Stephen G. Waxman, Ph.D., M.D., professor of neurology, pharmacology and neurobiology, and his colleagues looked for clues at the source—postmortem spinal cord tissue from MS patients. In a study published in May in the *Proceedings of the National Academy of Sciences*, Waxman's team and researchers from the VA Connecticut Healthcare System in West Haven and University College London described the first observations in humans of key molecules that contribute to nerve fiber degeneration. These molecules, though produced to compensate for a short in the neural signaling circuit, ultimately—and ironically—initiate a series of events that cause nerve damage.

To relay signals to other neurons, healthy nerve cells are studded with sodium channels that open in succession along the nerve fiber to allow in surges of sodium when neurons become activated. To help propagate this signal, an outer coating of myelin insulates the nerve cells. But in those with MS, the myelin breaks down, causing a short in the signal circuit. Waxman and colleagues found that MS neurons compensate for this defect by overexpressing the sodium channel Nav1.6—normally present only at small regions called nodes of Ranvier—all along the nerve fiber to improve the signal relay. However, the atypical Nav1.6 expression appears to cause more harm than good, as it coincides with regions of axon injury.

There are at least 10 types of sodium channels in human nerve cells, each with a different task, Waxman explained. "It's as if you have 10 different types of batteries. Only the right batteries will make a device work properly." In this case, the cells are using the wrong batteries in the wrong place. The researchers observed that another protein called NCX, a sodium-calcium exchanger, is expressed near Nav1.6 sites. The aberrant placement and overabundance of Nav1.6 causes too much sodium to enter the cells. Overexpression of NCX adjacent to Nav1.6 channels presumably flushes out the excess sodium and replaces it with calcium. But too much calcium provokes molecular chain reactions, sending cells into activity overdrive that results in cellular damage and disease symptoms.

In a field long dominated by immunobiologists, Waxman is enthusiastic about the contributions to the understanding of MS that he and his neurobiologist colleagues are making. "We are chipping away at the disease molecule by molecule, and we are understanding more about the disease process," he said. Based on his research, Waxman is eager to try targeting the neurons for treatment; all approved MS therapies currently target the immune system. Consistent with his research findings, he said, "Drugs that block sodium channels prevent axonal death." Consequently, he is involved in an upcoming clinical trial that will test sodium prove its efficacy, curcumin may be the first cystic fibrosis drug that treats the cause of the disease rather than just the symptoms.

—Kara Nyberg