

**Research Now** is a quarterly feature of **Momentum**, produced by the Society's Research and Clinical Programs Department.

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## Investigating ion channels for MS symptoms, and even neuroprotection

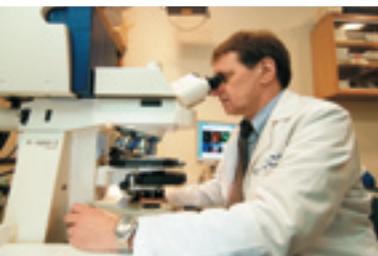
by Sara Bernstein

**A**t this writing, Fampridine-SR (proposed name Amaya, from Acorda Therapeutics) has been recommended for approval to improve walking speed in MS by an advisory committee of the U.S. Food and Drug Administration. If approved it will be the first therapy approved specifically to treat a symptom in people with MS. But this drug also tops off years of preclinical research on “ion channels” and how blocking them may provide a strategy for treating

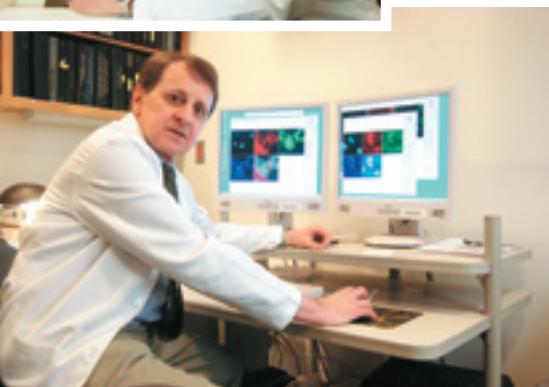
MS symptoms, or even protecting nerves from damage.

Ion channels (see illustration) are tiny pores that allow charged particles—for example, sodium, potassium and calcium ions—to pass in and out of a cell. These channels are made up of protein molecules that assemble to form a water-filled tunnel across the cell's protective membrane.

In nerve cells, ion channels work with extreme precision: Sodium channels open for a fraction of a second to allow just enough sodium in to trigger a nerve impulse. The impulse is then transmitted to the next cell, exactly the same way, and so on throughout the body. Potassium channels do the opposite and



**Stephen G. Waxman, MD, PhD (Yale University, New Haven, CT) was awarded the 2002 John Dystel Prize for MS Research by the National MS Society and the American Academy of Neurology for his groundbreaking findings on ion channels and MS.**



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act as a brake. Working together with sodium channels they regulate the impulse.

### **Does ion channel dysfunction play a role in MS?**

Missteps in the tightly run microcosm of ion channels can have dramatic effects on nerve cell function. Could such ion channel abnormalities contribute to MS? Stephen G. Waxman, MD, PhD (Yale University, New Haven, Conn.) was awarded the 2002 John Dystel Prize for MS Research by the National MS Society and the American Academy of Neurology for his groundbreaking findings on ion channels and MS.

Dr. Waxman demonstrated that the loss of myelin (the substance that surrounds nerve fibers and is a target of the immune attack in MS) exposes parts of nerve fibers that do not contain

enough sodium channels. This is important because it shows that the exposed, demyelinated part of the nerve fiber does not have the ability to produce nerve impulses. Dr. Waxman went on to show that, remarkably, the demyelinated nerve fiber can rebuild itself, acquiring enough sodium channels to conduct nerve impulses again. This “plasticity” contributes to remissions in MS. **Proceedings of the National Academy of Sciences (PNAS) USA** 2004;101:8168–8173

Dr. Waxman also showed that in MS the wrong type of sodium channels are produced in a part of the brain called the cerebellum (which controls coordination of movement), finding evidence that this can impair movement in MS. **PNAS USA** 2000;97:11598–602

### **Channel blockers to treat MS symptoms**

The work of Dr. Waxman and others led to development of treatments that might improve neurological function in MS by altering ion channel activity. Several channel blockers, such as phenytoin and carbamazepine, approved for other indications, are now used for MS pain.

Fampridine-SR is another such treatment—a sustained-release formula of 4-aminopyridine, which blocks potassium channels. When exposed by myelin damage, potassium ions leak out, causing the nerve impulse to “short circuit.” Fampridine-SR closes the exposed channels, and enables the nerve fiber to transmit nerve impulses again.

Early trials of this potassium-blocking approach in people with MS were supported by the Society, including a clinical trial by Christopher Bever, MD (University of Maryland, Baltimore). This trial used Fampridine’s chemical cousin, 3,4-diaminopyridine. In later clinical trials, a significantly greater proportion of people who responded to the therapy had a consistent improvement in walking speed compared to those who took a placebo.

### **The search for channel blockers to treat MS symptoms continues**

Investigators in France are seeking to determine whether 3,4-diaminopyridine can improve fatigue in 125 people with MS. Read more at [www.clinicaltrials.gov/ct2/show/NCT00190268](http://www.clinicaltrials.gov/ct2/show/NCT00190268). A phase II study is ongoing to determine whether oral nerispiridine—a potassium and sodium channel blocker—can improve walking speed in more than 300 people with all types of MS. The study is sponsored by Sanofi Aventis. Read more at: [www.clinicaltrials.gov/ct2/show/NCT00811902](http://www.clinicaltrials.gov/ct2/show/NCT00811902).

## Channel blockers for neuroprotection

Dr. Waxman's research has shown even more potent ramifications for the role of ion channel dysfunction in MS, by demonstrating a strong association between sodium channel abnormalities and nerve fiber damage in mice with the MS-like disorder EAE. **Brain** 2004;127:294–303

Nerve fiber damage contributes to the progression of disability in MS. So, can channel blockers protect nerve cells, and possibly prevent MS progression? Dr. Waxman administered phenytoin to mice with EAE, which protected nerve fibers from damage for up to 180 days. **Brain** 2006;129:3196–208

Ion channels are composed of several subunits. Lori Isom, PhD (University of Michigan, Ann Arbor), is exploring whether targeting subunits of a channel can help to develop better blockers. In her current Society-funded project, Dr. Isom's team has focused on the "beta 2" subunit; mice lacking the gene that instructs the building of this subunit had significant decreases in nerve fiber loss and degeneration during the course of EAE.

**Molecular and Cellular Neuroscience** 2009;40:143–55 They are currently examining how to "knock down" the activity of this gene in the spinal cord using experimental gene therapy.

In 2009, disappointing results were reported in a study testing the neuroprotective effects of a

channel blocker in people with MS. Raj Kapoor, MD, (National Hospital for Neurology and Neurosurgery, Queen Square, London) and colleagues studied the epilepsy drug lamotrigine in 120 people with secondary-progressive MS. The primary goal of the trial was to determine whether this drug (which may block sodium channels) could slow or stop the loss of brain tissue volume. The results suggested that tissue volume actually **decreased**, although the fact that decreases were recovered when treatment was stopped suggested that volume loss may have been related to the drug's strong anti-inflammatory nature. Surprisingly, participants taking lamotrigine improved in walking speed, although the study was not designed specifically to measure this as a primary outcome.

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The neuroprotective potential of lamotrigine is still under study in combination with interferon beta-1a, in a Swiss study of nearly 90 people with MS. Read more at [www.clinicaltrials.gov/ct2/show/NCT00917839](http://www.clinicaltrials.gov/ct2/show/NCT00917839).

The Society is funding another effort to explore neuroprotective effects in a drug that blocks sodium channels and is approved to treat ALS (Lou Gehrig's disease). Emmanuelle Waubant, MD, PhD, and investigators at the University of California, San Francisco, are study-

ing the possible nerve-protecting effects of oral riluzole (Rilutek) in people at high risk for MS or early MS, when combined with Avonex (interferon beta-1a). Read more at [www.clinicaltrials.gov/ct2/show/NCT00501943](http://www.clinicaltrials.gov/ct2/show/NCT00501943).

## Another angle

K. George Chandy, MD, PhD (University of California, Irvine) has taken another view of how ion channels contribute to MS. He and colleagues are focusing on ion channels on the surface of immune T cells, thought to lead the immune-system attack against the nervous system. Ion channels on T cells control the influx of charged particles and allow T cells to become activated. In research supported by the Society, Dr. Chandy's team successfully prevented and treated EAE in rats by blocking "Kv1.3," a specific T cell channel through which ions enter the cell.

Dr. Chandy's team formed a company, Airmid Incorporated, to develop Kv1.3 blockers as a strategy for MS and similar diseases. Kineta, Inc. acquired this portfolio in July 2009, and according to its Web site, plans to bring an MS drug to clinical trials in 2010.

Although the true potential of ion channel blockers to help people with MS has not yet been reached, this strategy carries potential for stopping symptoms, restoring function and even protecting against nervous system damage in people with MS.

