

# Calming the excitement in ALS

Jonathan D. Glass, MD

Correspondence to  
Dr. Glass:  
jglas03@emory.edu

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The concept of excitotoxicity, first established by the pioneering work of John Olney,<sup>1</sup> traditionally has been applied to lesions of the CNS, focusing mostly on glutamate as a neurotoxic excitatory amino acid neurotransmitter. Indeed, glutamate excitotoxicity remains one of the best-supported theories for motor neuron death in amyotrophic lateral sclerosis (ALS),<sup>2</sup> and was the pharmacologic inspiration for riluzole, which remains the only drug proven to slow the course of ALS.<sup>3</sup> The excitotoxic model of disease can be appropriately extended to the peripheral nervous system (PNS), where overactivity of peripheral axons leads to symptoms of fasciculations and cramping. However, the increased firing of peripheral axons could also result in antidromic stimulation of parent motor and sensory neurons, resulting in increased excitatory activity and possibly excitotoxic injury. In this model, therapeutic interventions are directed at reducing axonal firing, which can be accomplished by blocking sodium channels.

In this issue of *Neurology*®, Weiss et al.<sup>4</sup> report on a phase 2 trial of the sodium channel blocker mexiletine in patients with ALS. The therapeutic basis for this intervention is to lessen the pathologic firing of peripheral axons and thus slow disease by reducing excitotoxic neuronal damage. However, as with all phase 2 trials, this was designed and powered to investigate safety and tolerability of the drug, and there was little expectation that efficacy in slowing disease progression would be found. Driven by a suggestion from a colleague, these investigators also included secondary outcome measures of frequency and intensity of muscle cramps, and identified a strong dose-response relationship, supporting their conclusion that mexiletine reduces cramping in ALS, which represents a potentially important therapeutic option for patients with this painful symptom. The trial did not include the modern neurophysiologic technique of threshold tracking, a method that measures the inherent excitability of axons, which could provide correlative evidence of reduced sodium conductance associated with the observed improvement in symptoms. Using threshold tracking, Kuwabara et al.<sup>5</sup> demonstrated that mexiletine reduces sodium

conductance in peripheral nerve axons. This Japanese group also completed a trial of mexiletine in ALS using the same 300 mg/d dose as the American trial. Interestingly, they could not measure the predicted reduction in axonal sodium current in response to mexiletine and also did not observe any improvement in disease progression.<sup>6</sup> There was no measurement of cramping in the Japanese study, and so a direct relationship among mexiletine, sodium conductance, and cramping remains to be demonstrated.

The question of excitatory mechanisms in the pathophysiology of ALS remains a major topic of interest. The hyperactivity of individual motor units is easily observed in the PNS, manifesting clinically in the prominence of muscle fasciculations and cramps in people with ALS. Case reports (and personal experience) of patients presenting with prominent fasciculations without weakness or evidence of denervation with needle EMG, but who later develop definitive ALS, indicate that hyperexcitability may precede axonal or motor neuron death. Some authors hypothesize this as a form of excitotoxicity that may be an initial driver of disease in ALS.<sup>7,8</sup> For the CNS, there is no easily observable indication of neuronal hyperexcitability in the standard clinical examination. However, transcranial magnetic stimulation consistently demonstrates cortical hyperexcitability as a feature of ALS.<sup>9,10</sup> This technique continues to be used to demonstrate abnormalities in upper motor neuron circuits that underlie spasticity, weakness, and fatigue in ALS.<sup>11</sup>

In the laboratory, models of genetically based ALS show that motor neurons either carrying disease mutations or exposed to astrocytes expressing disease mutations become hyperexcitable and die. Reducing repetitive firing by blocking sodium channels (as is the proposed mechanism of action with mexiletine) protects against motor neuron death.<sup>12</sup> Recent work using induced pluripotent stem cell (iPS)-derived motor neurons generated from patients with ALS again demonstrates the intrinsic hyperexcitability of ALS motor neurons. In the case of iPS-derived neurons carrying disease-causing *SOD1* mutations, the hyperexcitability and associated neuronal death was

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From the Department of Neurology, Emory University School of Medicine, Atlanta, GA.

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ameliorated by correcting the mutant gene, suggesting that hyperexcitability was caused by the presence of mutant *SOD1*, and that hyperexcitability underlies the mechanism of death.<sup>13</sup> Protection was also provided by the anticonvulsant retigabine, which acts by reducing excitability through hyperpolarizing neurons via activation of the rectifying potassium current (rather than blocking the sodium current). This work is the basis of a new clinical trial testing retigabine in patients with ALS, both to reduce hyperexcitability and slow disease progression.

As with many clinical, physiologic, and pathologic observations in neurodegenerative diseases, we are faced with the question of correlation vs causation. Does hyperexcitability lead to excitotoxicity in ALS? Will reduction of neuronal and axonal firing rates just reduce symptoms (i.e., cramps, fasciculations, and possibly spasticity), or will this approach protect against neuronal degeneration? In vitro models suggest the latter, but we must move forward to the clinic with cautious optimism given our long experience of failures in the transition from bench to bedside in ALS. Nevertheless, the observation of reduced cramping with mexiletine is a positive result for our patients. A new phase 2 trial of mexiletine funded by the ALS Association and the Northeast ALS Consortium will hopefully confirm the therapeutic effects on cramping, but will also correlate any clinical outcomes with electrophysiologic measures of neuronal excitability in the PNS and CNS. Any observation of a slowing of clinical progression would be a much-appreciated bonus.

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