Mouse Model of Epileptic Syndrome Yields Discoveries That May Illuminate Autism Spectrum Disorders

by Sally James

A team of researchers from the University of Washington discovered some surprising findings in research on mice bred to have genetic defects that cause a disorder known as Dravet Syndrome. Team leader, William Catterall, Ph.D., helped to explain the findings during an interview. The findings were published in the journal Nature in September. Catterall is Professor and Chair of the Department of Pharmacology and a research affiliate at the Center on Human Development and Disability.

Catterall has spent much of his career exploring and unraveling just how the brain uses sodium channels to send electrical signals along nerve cells, and the implications of this pathway in many human diseases. The mice in this experiment had a mutation in the gene Scn1a that disabled one of the known brain sodium channels, called Nav1.1. As a result of the mutation, that failed sodium channel gave the mice symptoms of the human disease, Dravet Syndrome, which strikes children in infancy. The syndrome is rare, with about one in 20,000 children in the United States born with the disorder. For children with Dravet Syndrome, the disease begins with epileptic seizures at 6-9 months of age and evolves to include intellectual disabilities as well as a behavioral pattern similar to those observed in children on the autism spectrum. In addition to cognitive deficits, the autistic-like behaviors include hyperactivity, problems in social interaction, and anxiety.

In the brain, there are two broad classes of nerve cells—excitatory neurons that activate the electrical signaling of neighboring nerve cells and inhibitory neurons that inhibit neighboring nerve cells. The inhibitory neurons use the chemical neurotransmitter GABA (gamma-aminobutyric acid) to inhibit their neighbors. The Dravet Syndrome mutation in the mice used in this study causes a failure of electrical signaling and loss of inhibitory neurotransmission via GABA in the inhibitory neurons in two important parts of their brains—the hippocampus and the cerebral cortex. This impairment of the normal function of inhibitory neurons allows the excitatory neurons to overwhelm the brain with electrical signals thereby causing epilepsy and related problems.

One way to think about this defect in brain signaling is with a crude analogy. Automobile traffic has red lights and green lights. In the brain there are inhibitory signals (red) and excitatory signals
“Imagine New York traffic at rush hour with only green lights,” Catterall said, to try to illustrate what kind of chaos exists if the sodium channels responsible for the inhibitory signaling are disrupted. The mutation that causes Dravet Syndrome falls into this category, because it prevents the normal function of inhibitory neurons but does not affect excitatory neurons. There has been much recent research to add support to the hypothesis that an imbalance of excitatory and inhibitory signals may be at the root of some syndromes that result in autistic behaviors, he explained. Among these are Rett Syndrome and Fragile-X Syndrome. His team chose the Dravet Syndrome model for these mice hoping to find further discoveries about that relationship. But the team was not prepared for the biggest surprise in one of their experiments.

There are medications already approved and prescribed to children with Dravet Syndrome that aim to reduce the severity and number of seizures. One of these is clonazepam (Klonipin). As part of an experiment, the researchers gave the mice a very low dose of this drug to observe the results. After giving mice only 1/10th of the dose that would be equivalent to a normal dose for a human patient, they saw a reversing of the symptoms of cognitive deficit and autistic-like behaviors. “We saw complete reversal and rescue” of these behaviors, Catterall said. “We didn't expect that.” This was one of the genuine “aha moments” in research, he said.

The mice—which had exhibited anxiety, cognitive, and social deficits—behaved as if they were normal “wild-type” mice, and not as if they had the mutation. This result leads to speculation that sodium channels may play an important role in other neurodevelopmental disorders. It also raises hope that the medications in the same family as clonazepam—which includes drugs such as Ambien and Valium—may one day be of value for children with Dravet Syndrome and possibly disorders along the autism spectrum.

In addition, Catterall emphasized that many caregivers of children with Dravet Syndrome feared that the seizures caused permanent irreversible damage to the brains of their young children, and that some of the symptoms observed were due to permanent changes. The mouse model—which showed reversibility of those symptoms with drug treatment—provides hope that not all the damage is permanent. Catterall is applying for research grants to begin a clinical trial on children with Dravet Syndrome. This trial would probably take about two years to complete. There are many more questions and many years of experiments remaining before any routine low-dose treatment with benzodiazepines is practical for human patients. But the discovery does provide a crucial window into a new way to approach treatment of problems that are common to children with a variety of neurodevelopmental disorders.