NEWS

Neurons struggle to spike without fragile X gene

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Neurons deep in the prefrontal cortex of fragile X model mice have trouble generating the electrical spikes needed to transmit information, according to a new **study**. The difficulty originates from faulty sodium channels.

Fragile X syndrome, one of the leading genetic causes of autism, results from mutations in the gene **FMR1**. People with the condition often have difficulty with executive-function skills, such as working memory and planning. The new study may explain why, says **Randi Hagerman**, medical director of the MIND Institute at the University of California, Davis: The disruption to signals propagating through the prefrontal cortex may impede the region's role in coordinating communication among other parts of the brain.

Some drugs that regulate sodium channels, such as the **diabetes drug** metformin, are already approved for use in people.

“This is a great animal model to look at the effects of medication,” says Hagerman, who was not involved in the new work.

Mutations in the autism-linked gene **SCN2A**, which encodes a protein for the sodium channel Nav1.2, also suppress dendritic spikes, researchers **previously showed** in mice. The cellular mechanism for channel disruption is different between the models, but it’s possible that multiple genetic causes of autism “coalesce around sodium channel disfunction,” says **Darrin Brager**, research associate professor of neuroscience at the University of Texas at Austin and lead investigator on the FMR1 study. “The same channel is altered, and that’s changing the way the

cells are able to integrate information and transmit it.”

Brager and his team focused on cortical layer 5 neurons that integrate information from upper layers and transmit signals to other parts of the brain. They recorded activity from these cells in thin slices of prefrontal cortex from mice lacking both copies of FMR1.

To maintain a signal over long distances, the neurons typically generate a dendritic spike that carries information to the cell body, which then triggers an action potential to pass the signal along. But neurons from the fragile X mice, the researchers found, required stronger electrical input than control neurons to generate both dendritic spikes and action potentials.

Fewer sodium ions flowed through the channels that generate dendritic spikes in fragile X cells than in controls. And the membranes surrounding fragile X cells had less ability to transmit electrical signals, suggesting that they had fewer sodium channels overall, Brager says.

The findings were published in *The Journal of Physiology* in January.

The team is currently probing how FMRP — the protein encoded by FMR1 — regulates the sodium channel, Brager says, which could help determine if this mechanism is specific to fragile X syndrome.

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