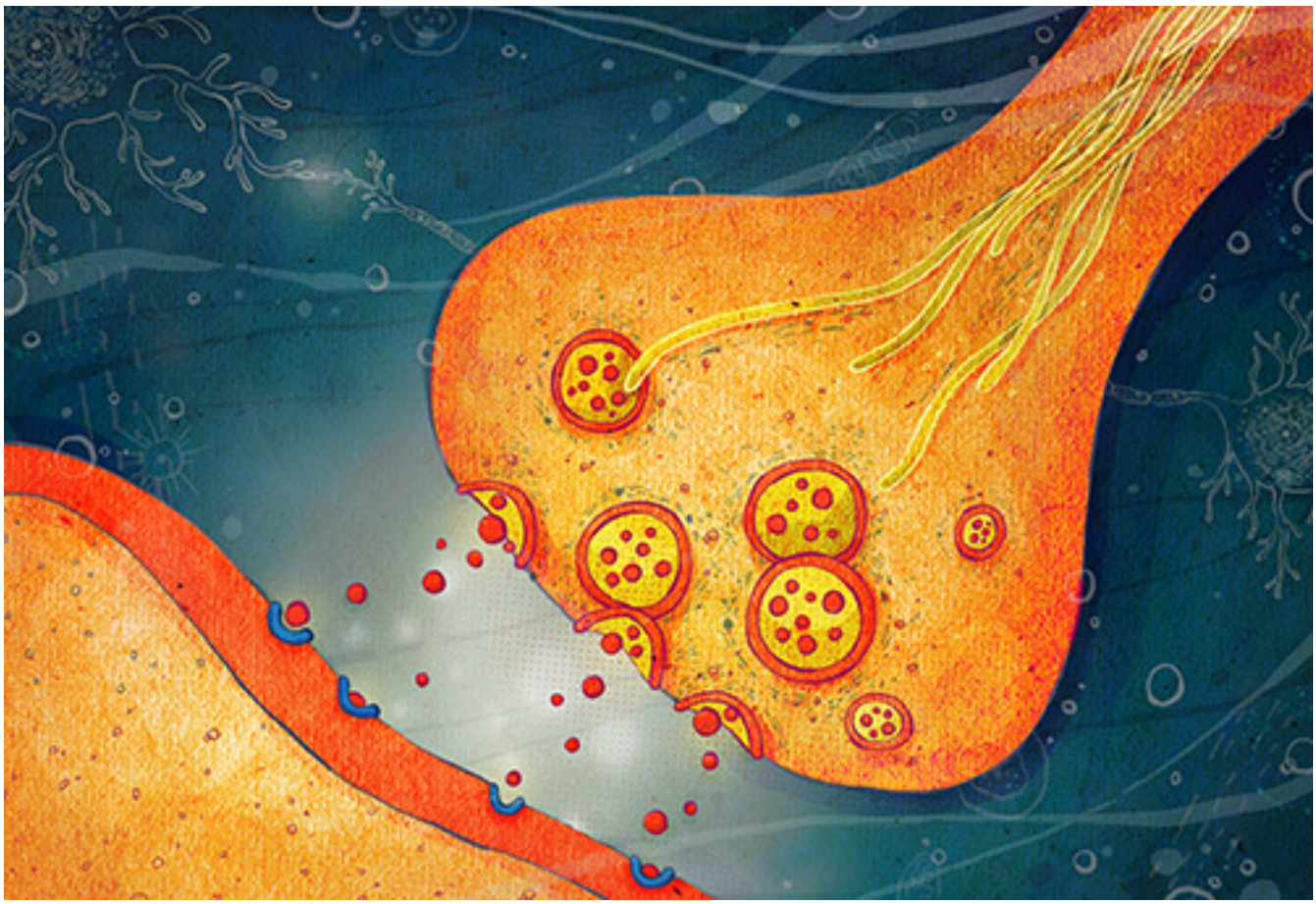
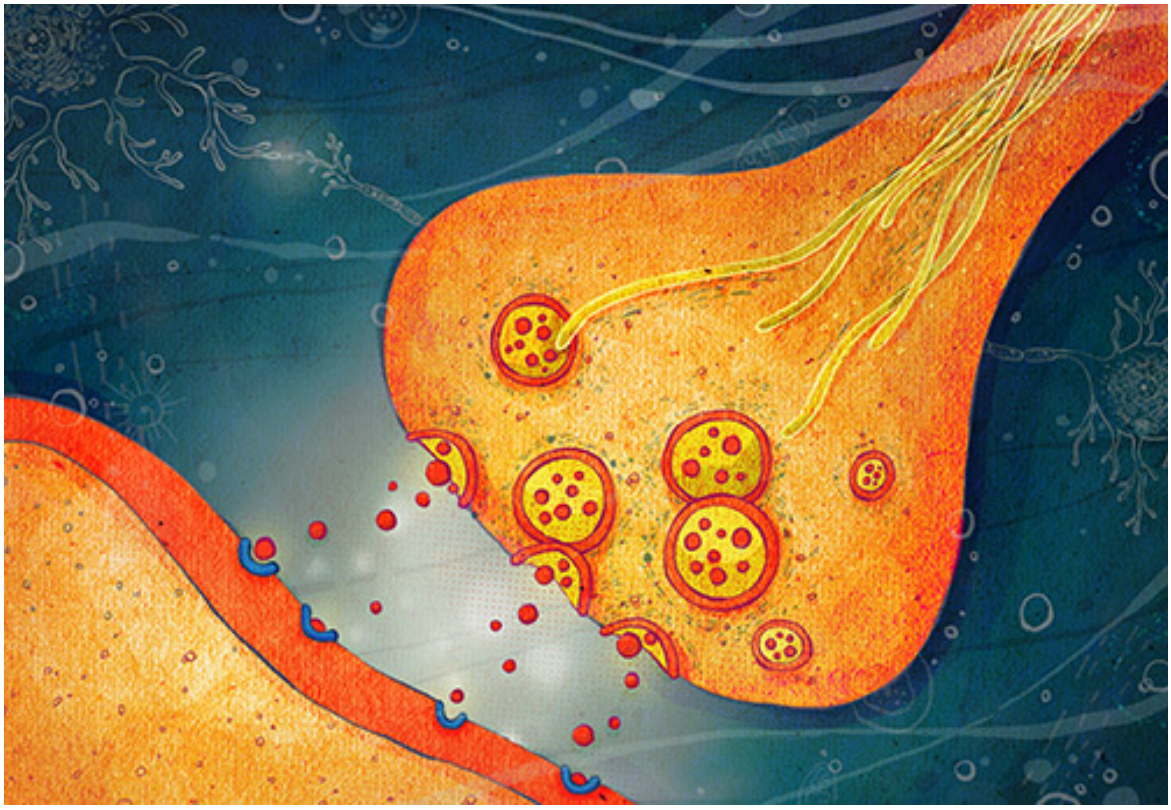
NEWS

Targeting potassium channel eases autism symptoms in mice

BY **NICHOLETTE ZELIADT**

17 NOVEMBER 2014





Julia Yellow

Lowering the levels of a certain ion channel reverses autism-like behaviors in a mouse model of **fragile X syndrome**, according to unpublished results presented yesterday at the **2014 Society for Neuroscience annual meeting** in Washington, D.C.

People with fragile X syndrome, which is a common inherited cause of autism, often have intellectual disability, hyperactivity, anxiety and hypersensitivity to sensory stimuli. Mice that lack FMRP, the fragile X protein, recapitulate many of these same features.

In the new study, researchers looked at the effect of FMRP loss on the expression of other genes. They found that mice lacking FMRP show increased levels of Kv4.2, a protein that functions as a channel for potassium ions to traverse out of neurons.

The channel is also expressed at higher levels in postmortem brain tissue from people with fragile X syndrome than in tissue from controls.

“That got our attention, because it’s a very interesting and very critical channel,” says Hye Young Lee, a postdoctoral fellow in **Lily Jan**’s lab at the University of California, San Francisco, who presented the work.

Kv4.2 regulates communication between neurons and the strengthening or weakening of neuronal connections over time — a process known as synaptic plasticity.

Mice lacking FMRP show deficits in a form of synaptic plasticity known as long-term potentiation (LTP), which strengthens neuronal connections. Bathing brain tissue from the fragile X mice with hpTX2, a toxin that blocks Kv4.2, restores LTP, the researchers found.

The researchers then generated mice that lack FMRP and have half the usual amount of Kv4.2. They assessed the mice using a wide variety of behavioral tests that measure fragile X symptoms. They found that partial loss of Kv4.2 reverses many of the mice’s autism-like behaviors.

For example, in a test of **repetitive behaviors**, fragile X mice with normal levels of Kv4.2 compulsively bury more marbles than controls do. And in tests of social behavior, they spend less time interacting with other mice and are slower to initiate ultrasonic vocalizations, a form of social communication. These behaviors are also frequently seen in mouse models of autism.

By contrast, mice with half the normal levels of Kv4.2 perform the way controls do on these tasks. However, partial loss of Kv4.2 has no effect on hyperactivity, anxiety and deficits in learning and memory.

“Some of the behaviors got rescued, and certainly it is interesting that almost all of the behaviors were autistic-like behaviors,” Lee says. Compounds that block Kv4.2 may have therapeutic potential for both autism and fragile X syndrome, she says, but there are no candidates available thus far. Her team plans to screen libraries of small molecules for their ability to block Kv4.2.

Lee says she does not know why partial loss of Kv4.2 reverses only certain behaviors in the animals. She speculates that it may be because unlike FMRP, which is expressed everywhere, Kv4.2 is found in only certain regions of the brain. “We think there is a certain circuit disruption for selective behaviors,” she says.

*For more reports from the 2014 Society for Neuroscience annual meeting, please **click here**.*