Lithium may treat behavior linked to autism gene
27 April 2020, by Peter Hess

Case studies of people with Phelan-McDermid syndrome also suggest that lithium eases behavior problems associated with the condition^2.

Previous work has shown that SHANK3 helps stabilize neuronal circuits by adjusting excitatory and inhibitory signaling like a thermostat. This process, called homeostatic plasticity, allows neurons to respond to changes in sensory input.

The new study suggests the gene controls this thermostat by regulating how frequently neurons fire and how they adjust the electrical currents flowing through them. SHANK3 loss or mutation prevents neurons from adapting to changes in sensory input.

"What we've shown is there's this cellular mechanism, and loss of that mechanism is a direct result of a loss of SHANK3," Turrigiano says.

**Firepower**

The team first recorded electrical activity in rat neurons in which SHANK3 expression was partially disrupted. They artificially blocked the neurons' ability to fire. The mutant neurons' rate of firing did not return to its original range afterward as it did in control cells, the team found.

The neurons also responded with less electrical activity than controls did when the researchers blocked and then restarted electrical currents. This suggests the mutant neurons had lost their ability to adjust the current flowing through them.

Excitatory neurons in the cortex called pyramidal cells are most strongly affected. Lithium restored the cells' ability to adjust both their firing rates and how much current they carry.

To examine how neurons in mice lacking SHANK3 respond to changes in sensory input, the team implanted electrode arrays into the visual cortex of...
the mutant mice and controls and glued one eye shut in each mouse.

Over the following three or four days, the neurons in both groups of mice decreased how frequently they fired. But the decrease in the mutant mice was more gradual, suggesting that they take longer to adjust.

Neurons in the control mice returned to their typical firing rate two days after the rate had slowed to its lowest level, presumably because the mice's brains had adapted to the loss of vision in one eye. But in the mutant mice, the neurons never returned to their original firing rates, indicating that without the gene, their brains could not adapt.

The mutant mice also groom themselves excessively, a behavior that is thought to align with obsessive or repetitive behaviors in people. To the researchers’ surprise, lithium stopped this behavior entirely. The work appeared in March in Neuron.

**Treatment potential**

The findings support the idea that lithium may help treat people with SHANK3 mutations, and perhaps those with other forms of autism as well, says Jean Martin Beaulieu, associate professor of psychiatry and neurosciences at the University of Toronto in Canada, who was not involved in the study.

However, he says, the study does not prove that the problems with homeostatic plasticity cause the repetitive behavior. Overgrooming is a complex behavior involving multiple brain areas, he says, whereas the study examined only the visual cortex.

It is also unclear whether lithium acts directly on SHANK3 or on some other target in the circuit, says Thomas Bourgeron, professor of genetics at the Institut Pasteur in Paris, France, who was not involved in the study.

Turrigiano says the loss of SHANK3 may be just the first step in a process that leads to neurons’ inability to adapt to sensory input. Identifying which part of that process lithium corrects may point to new targets for treatment, she says.