NEWS

Molecular mechanisms: Enzyme blockers help fragile X mice

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The mood stabilizer lithium and two other drugs that block an enzyme called GSK-3 reverse cognitive deficits in a mouse model of **fragile X syndrome**, according to two studies published in August and September[1,2].

Lithium disables GSK-3, an enzyme that regulates the migration of neurons and other aspects of brain development, and is overactive in the hippocampus of fragile X mice. The **drug alleviates a suite of neuronal and behavioral deficits** in these animals, including hyperactivity, susceptibility to seizures and **irregular neuronal signaling**. It has also shown promise in children and adults with fragile X syndrome.

Lithium has many molecular targets, however, so it has several side effects, such as excessive urination. A drug that specifically targets GSK-3 might be more clinically useful. Also, although cognitive deficits are the main symptoms of fragile X, animal studies have not consistently probed the effects of GSK-3 blockade on cognition.

In the new work, researchers tested whether lithium, TDZD-8 and VP0.7 — two inhibitors that target only GSK-3 — can improve cognition in fragile X mice.

In the first study, after identifying three cognitive deficits in fragile X mice, the researchers gave nine adolescent mice (aged 4 to 8 weeks) and ten adult mice (aged 8 to 12 weeks) lithium by adding it to their diet for four weeks[1].

The drug reversed the deficits in both age groups, they found. However, the deficits returned after four weeks without treatment. The study was published 8 August in *Genes, Brain and Behavior*.

In the second study, published 13 September in *Biological Psychiatry*[2], the researchers injected

adult mice with a single dose of GSK-3 inhibitor or saline solution. Both inhibitors reversed the cognitive deficits. They also quieted the overactive remodeling of **synapses**, or neuronal junctions, in the dentate gyrus, an area of the hippocampus thought to regulate memory formation.

The results support GSK-3 as a good therapeutic target for treating fragile X syndrome, the researchers say.

References:

1. King M.K. and R.S. Jope *Genes Brain Behav.* Epub ahead of print (2013) **PubMed**

2. Franklin A.V. *et al. Biol. Psychiatry* Epub ahead of print (2013) **PubMed**