NEWS

Molecular mechanisms: Mutations link mood system to autism

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Two different autism-linked mutations in the same gene implicate the endocannabinoid system, which regulates appetite, mood and memory, in autism, according to a study published 8 May in *Neuron*[1].

Neuroligin-3 (NLGN3) is a member of a family of proteins that help organize connections between neurons at their junctions, or **synapses**. Studies have **linked NLGN3 to autism**. An individual with autism may either have a mutation that alters a single amino acid in the gene, such as NLGN3-R451C, or lack the entire gene (NLGN3-KO).

Form vs. function: A neuron from a mouse with a NLGN3 mutation has a normal shape, but altered signaling.

NLGN3-R451C and NLGN3-KO are known to sometimes have opposing effects on neurons. The researchers explored whether they also have any shared effects, which might explain their common link to autism. They looked at signals between neurons in brain slices from mice with either NLGN3-R451C or NLGN3-KO.

The researchers focused on inhibitory synapses, which dampen neuronal activity, because NLGN3-KO is known to influence them. They looked at the signals sent from two types of inhibitory neurons — those that express either the chemical messenger parvalbumin or cholecystokinin (CCK). These inhibitory neurons release chemical messengers, primarily gamma-aminobutyric acid (GABA) that dampen the activity of the neurons they connect with.

In line with previous studies, the two mutations have the opposite effect on parvalbumin synapses:

NLGN3-KO strengthens the inhibition and NLGN3-R451C dampens it.

Surprisingly, however, both mutations enhance the inhibitory activity of CCK neurons, which function in the endocannabinoid pathway.

When CCK neurons normally bind endocannabinoids, they release less GABA, resulting in weaker inhibitory signals. The mutations cause deficits in a particular form of long-term endocannabinoid signaling called tonic signaling. This leads to extra GABA in the synapse and the boost in inhibition.

Studies have suggested that an **imbalance between excitatory and inhibitory signals** underlies autism. Levels of GABA and **genes that code for its receptor** have also been linked to autism.

References:

1: Földy C. *et al. Neuron* **78**, 498-509 (2013) **PubMed**