

NEWS

# Molecular mechanisms: Drug corrects excitable mouse brains

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Signal spikes: Mice lacking a receptor that mediates excitatory brain signals (left) have weaker coordinated brain activity than controls do (right).

A compound called baclofen restores the balance between different types of brain signals and alleviates autism-like behaviors in mice, according to a study published 17 July in *Translational Psychiatry*<sup>1</sup>. A related drug called arbaclofen **is in clinical trials** as a treatment for autism and **fragile X syndrome**.

One popular theory holds that the brains of people with autism have too many excitatory signals and too few inhibitory ones. This imbalance can make a brain prone to seizures, and may explain the **overlap between autism and epilepsy**.

Excitatory signals are mediated by several different classes of proteins, including NMDA receptors. Mutations in genes that code for NMDA receptors have been linked to both schizophrenia and autism<sup>2</sup>. Glitches in a number of other autism candidate genes, including **SHANK3**, **NLGN1**, **FMR1** and **NRXN1**, also lead to deficits in NMDA-mediated signaling.

In the new study, researchers engineered mice to have significantly fewer NMDA receptors than in controls. These mice have behavioral deficits reminiscent of autism: They socialize less than controls do, and perform poorly in a test of learning and memory.

The mutant mice also show elevated excitatory signaling, the study found. Compared with controls, they have up to 70 percent fewer parvalbumin interneurons, which inhibit signals in the brain. Also, pyramidal neurons, which generate excitatory signals, fire more readily than in controls.

The researchers also investigated gamma synchrony, an electrical measure of the coordinated activity of groups of neurons. This measure is known to spike during complex cognitive behaviors, suggesting that it represents the neural coordination required to accomplish these tasks.

The mutant mice have higher baseline gamma activity in the hippocampus, a brain region involved in learning and memory, than controls do. They also have lower gamma spikes after hearing a sound that typically induces gamma activity. Overall, these results lower the signal-to-noise ratio, and indicate weak coordination of brain activity during cognitive tasks, the researchers say.

The mutant mice with the highest baseline gamma activity are the least likely to engage in social interactions or to successfully navigate a maze, the study found.

Treatment with baclofen improves both the gamma activity patterns and social behaviors. Baclofen enhances inhibitory signals.

### References:

**1: Gandal M.J.** *et al. Transl. Psychiatry* **2**, e142 (2012) [PubMed](#)

**2: Gai X.** *et al. Mol. Psychiatry* **17**, 402-411 (2012) [PubMed](#)