

Boosting certain brain cells diminishes hypersensitivity in Fragile X mice

July 13 2023



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Boosting the activity of inhibitory interneurons in Fragile X mice reduced their hypersensitivity to sensory stimuli, according to a new *Neuron* study led by UCLA Health researchers.

Fragile X Syndrome, which is caused by a mutation in a [single gene](#), is the most common inherited form of intellectual disability and autism.

Many people with Fragile X are extremely sensitive to sights, sounds, and touch, among other sensory experiences.

Previous research found Fragile X [mice](#) have a lower density of parvalbumin (PV) [inhibitory interneurons](#), the main class of inhibitory neurons in the [cerebral cortex](#)—the region of the brain responsible for sensory processing. These neurons act like a brake on excitatory neurons to help them fire only when necessary.

Because autism symptoms first appear during the toddler stage and likely reflect changes in the brain that happened earlier, the researchers sought to establish when the reduced activity of PV interneurons was first apparent during [brain development](#) in mice—and whether intervention could help mitigate sensory hypersensitivity.

Researchers recorded neuronal activity in the brains of young mice during the first two weeks of life. They then sought to influence this activity through a novel drug compound that boosts the firing of PV neurons.

PV neurons

Researchers found that the density of PV neurons is indeed lower in Fragile X mice compared to controls—but even in mice as young as six days old. There were also greater numbers of dying PV neurons during [early development](#) in Fragile X mice, suggesting that these neurons are dying at a higher rate than what is considered healthy.

They also found that PV neurons in young Fragile X mice were unable to regulate the activity of excitatory neurons during the first two weeks of development, indicating that these neurons are functionally decoupled during this time. That could explain why researchers were able to restore PV neuron density by boosting PV neuron activity during this period of

development but could not restore the activity of excitatory neurons.

Researchers then administered a novel drug compound aimed at activating PV neurons in Fragile X mice during the third week of development. The treatment restored the ability of excitatory neurons to respond to touch, resembling how they function in healthy controls. It also reduced hypersensitivity to repeated touch, which is similar to what is known as tactile defensiveness in humans with Fragile X.

Potential treatment

While there are no existing treatments for the root cause of Fragile X, there are medications that address symptoms like anxiety, ADHD, or seizures. The new research suggests modulating the activity of PV neurons could be an effective approach to restoring circuit function.

"Our research is an example of how therapies that target circuit differences in neurodevelopmental conditions, like boosting the activity of inhibitory neurons in the brain, could help mitigate bothersome symptoms such as sensory hypersensitivity," said corresponding author Carlos Portera-Cailliau, MD, Ph.D., a professor of neurology and neurobiology at the David Geffen School of Medicine at UCLA. Nazim Kourdougli, Ph.D., a postdoctoral fellow in Portera-Cailliau's lab, is the first author.

Portera-Cailliau's lab will continue investigating how inhibitory neurons make synapses with excitatory neurons during development, and how the mutation in Fragile X affects this process. It will also test if the same drug compound can ameliorate other behavioral differences in Fragile X mice.

More information: Carlos Portera-Cailliau, Improvement of sensory deficits in fragile X mice by increasing cortical interneuron activity after

the critical period, *Neuron* (2023). DOI: [10.1016/j.neuron.2023.06.009](https://doi.org/10.1016/j.neuron.2023.06.009).
[www.cell.com/neuron/fulltext/S0896-6273\(23\)00468-3](https://www.cell.com/neuron/fulltext/S0896-6273(23)00468-3)

Provided by University of California, Los Angeles

Citation: Boosting certain brain cells diminishes hypersensitivity in Fragile X mice (2023, July 13) retrieved 21 May 2024 from
<https://medicalxpress.com/news/2023-07-boosting-brain-cells-diminishes-hypersensitivity.html>

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