Fragile X makes brain cells talk too much, research shows

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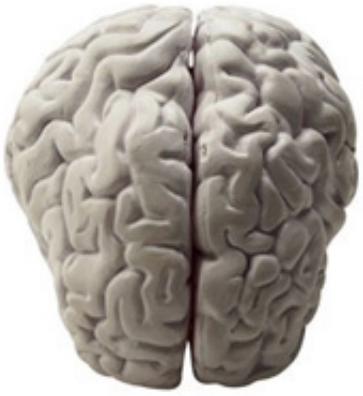

The most common inherited form of mental retardation and autism, fragile X syndrome, turns some brain cells into chatterboxes, scientists at Washington University School of Medicine in St. Louis report.

The extra talk may make it harder for brain cells to identify and attend to important signals, potentially establishing an intriguing parallel at the cellular level to the attention problems seen in autism.

According to the researchers, understanding the effects of this altered signaling will be important to developing successful treatments for fragile X and autism.

"We don't know precisely how information is encoded in the brain, but we presume that some signals are important and some are noise," says senior author Vitaly Klyachko, PhD, assistant professor of cell biology and physiology. "Our theoretical model suggests that the changes we detected may make it much more difficult for brain cells to distinguish the important signals from the noise."

The findings appear Feb. 20 in *Neuron*.

Fragile X is caused by mutations in a gene called Fmr1. This gene is found on the X chromosome, one of the two sex chromosomes. Females have two copies of that chromosome, while males only have one. As a result, males have fragile X syndrome more often than females, and the effects in males tend to be more severe.

Symptoms of fragile X include mental retardation, hyperactivity, epilepsy, impulsive behavior, and delays in the development of speech and walking. Fragile X also affects anatomy, leading to unusually large heads, flat feet, large body size and distinctive facial features. Thirty percent of fragile X patients are autistic.

Scientists deleted the Fmr1 gene many years ago in mice to create a model of fragile X. Without Fmr1, the mice have abnormalities in brain cells and social and behavioral deficits similar to those seen in human fragile X.

According to Klyachko, nearly all fragile X mouse studies in the past two decades have focused on how Fmr1 loss affects dendrites, the branches of nerve cells that receive signals. In contrast, his new study finds significant changes in axons, the branches of nerve cells that send signals.

Normally, signals travel down the axon as surges of electrical energy.

These surges only last for tiny fractions of a second, briefly causing the axon to release compounds known as neurotransmitters into the short gap between nerve cells. The neurotransmitters cross the gap and bind to their receptors on the dendrite to convey the signal.

When Klyachko monitored electrical surges along axons in the fragile X mice, though, he discovered that they lasted significantly longer. This caused release of more of neurotransmitters from the axon. When it should have stopped talking, the axon continued to chatter.

"The axons are putting out much more neurotransmitter than they should, and we think this confuses the system and overloads the circuitry," Klyachko explains. "It may also create problems in terms of brain cells using up their resources much more quickly than they normally would."

Infusing synthetic copies of the gene's protein, called FMRP, into brain cells from the mouse model rapidly restored the electrical surges to their normal length.

Additional experiments revealed that FMRP works by interacting with one of the biggest channels on the surfaces of axons. These channels let electrically charged potassium ions into the axons, helping to shape and control the duration of the electrical surge.

In healthy brain cells, the main function of these channels is to prevent the electrical surge from getting too long. With FMRP gone, the channel is active for a shorter time, prolonging the surge and overwhelming the dendrite with too much chatter.

Klyachko and his colleagues are now studying the connections between FMRP and the channel it interacts with in axons. They hope to learn more about how information is encoded and processed at the level of

individual brain cells. These insights one day may help clinicians better diagnose and treat many kinds of mental disorders.

More information: Deng P-Y, Rotman Z, Blundon JA, Cho Y, Cui J, Cavalli V, Zakharenko SS, Klyachko VA. FMRP regulates neurotransmitter release and synaptic information transmission by modulating action potential duration via BK channels. *Neuron*, Feb. 20, 2013.

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