NEWS

Fragile X protein linked to potassium channels

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Mouse models of fragile X syndrome show defects in two kinds of potassium channels — ubiquitous pores that control the flow of electrical current across neurons — in a brain area that processes sound, according to two papers published this summer.

The syndrome results from the absence of the fragile X mental retardation protein, or FMRP, often leading to mental retardation, delayed speech and autism. Although it is a little-studied phenomenon, anecdotal reports have shown that many people with fragile X syndrome are particularly sensitive to loud sounds[1] and have fluctuations in their speech[2]. An estimated one in four people with the syndrome are also prone to epilepsy[3].

The new studies suggest that unchecked signals from potassium channels could explain why people with the disorder have trouble filtering a barrage of auditory information.

"[The work] is the first to really look at the molecular and cellular basis of this auditory defect — that's one reason that it's a breakthrough," notes **Suzanne Zukin**, professor of neuroscience at Albert Einstein School of Medicine, who was not involved in the studies.

Another reason, she says, is that the findings might help researchers develop treatments, based on existing drugs that target potassium channels, to improve these problems.

Despite two decades of study, FMRP's **role in the neuron** is not fully understood. FMRP is known to bind to messenger RNAs — molecules that hold instructions for making proteins — in the nucleus and shuttle them to the distant ends, or synapses, of neuronal branches. During this process, FMRP prevents its cargo from being translated into proteins, only liberating it when it reaches the synapse.

Among the hundreds of messenger RNAs (mRNAs) that FMRP binds is one for Kv3.1, a potassium

channel. These protein pores use flowing potassium ions to control the voltage in a cell membrane, which in turns determines how readily a cell can fire. Mice missing FMRP have an abnormal distribution of Kv3.1 potassium channels in neurons of the brainstem, where sounds are processed, according to a report published 4 August in the *Journal of Neuroscience*[4].

In normal mice, sounds are filtered in a small part of the brainstem called the MNTB, or medial nucleus of the trapezoid body. High-frequency sounds are processed at one end of this region by neurons that carry large numbers of Kv3.1 channels. Low-frequency sounds are processed at the other end, where there are fewer Kv3.1 channels.

In the fragile X mutants, in contrast, this gradient is abolished, and there are high numbers of Kv3.1 channels across the region, the study found. Because FMRP normally represses the translation of Kv3.1 proteins, it makes sense that animals lacking FMRP show this abundance of channels.

Channel conversations:

Kv3.1 channels allow neurons to fire at extremely high rates, which helps decode loud and diverse sounds. But rapid firing can lead to mistakes in the timing of signals. Having too many Kv3.1 channels "means that even in a quiet environment, the cells will be firing too fast," says lead investigator **Leonard Kaczmarek**, professor of pharmacology at Yale University School of Medicine.

Another type of potassium channel, dubbed Slack, normally suppresses the firing of the cells. "Slack compensates for the errors in timing," Kaczmarek says. "It's a yin and yang."

Surprisingly, however**,** Slack also seems to function abnormally in the fragile X mutants. In a study published in the July *Nature Neuroscience*, Kaczmarek's group reported that FMRP binds directly to Slack and can activate the channel[5]. "If you don't have FMRP, you have much less of this potassium current that regulates the accuracy of timing," he says.

This is the first study to show that FMRP binds directly to a membrane protein, rather than primarily to mRNAs, as was assumed. "This is an important discovery," says **Gary Bassell**, professor of cell biology and neurology at Emory University, who was not involved with the work. "They're showing a novel and non-canonical function for FMRP that people hadn't been thinking about or pursuing."

FMRP clearly controls Slack, but Kaczmarek says Slack may in turn also regulate FMRP. "We think it's a two-way conversation," he says.

That interaction could explain how a neuron's firing patterns affect FMRP activity. When a neuron fires, more of FMRP's mRNA targets are translated compared with when the neuron is at rest. This ability to adapt to neuronal firing helps the brain rapidly learn new information.

Kaczmarek's team is creating mice that make less Slack to see if this changes how FMRP's mRNA targets are translated in the synapse.

The new findings also suggest that drugs that activate Slack may hold promise for treating sensory issues in those with fragile X syndrome.

Identifying drugs to treat the disorder is a top priority in the field, says Bassell. In the past few years, **promising clinical trials** of drugs that block mGluR receptors — which don't work properly in mouse models of fragile X syndrome — have garnered a great deal of attention.

"mGluR [drugs] are not going to correct all of the impairments in fragile X," Bassell says. Because there is significant variability in the disease, those with the disorder are likely to benefit from a cocktail of drugs. "That's the dream — that within the next few years, patients will have choices that can be tailored to them."

References:

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