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Deafness and seizures result when mysterious protein deleted in mice

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Scientists have discovered that mice genetically engineered to lack a particular protein in the brain have profound deafness and seizures. The finding suggests a pathway, they say, for exploring the hereditary causes of deafness and epilepsy in humans.

More broadly, the discovery provides an entry point for gaining new insight into the role of glutamate, the chemical messenger carried by the protein, says the team, led by scientists at the University of California, San Francisco. Glutamate is involved in virtually every brain function, including sensory perception, learning and memory.

The missing protein is a particular “vesicular neurotransmitter transporter,” a machine within nerve cells that ferries chemical messengers, or “neurotransmitters,” from the fluid-filled cytoplasm into vesicles that are positioned at the tips of nerve cells and serve to release neurotransmitters onto neighboring cells. Transporters and neurotransmitters work together to make possible essentially all neural communication in the brain.

While the neurotransmitter glutamate is the major excitatory messenger in the brain, the neurotransmitter GABA is the major inhibitory messenger, sending signals that reduce excitation and anxiety. Two other neurotransmitters, dopamine and serotonin, modulate the activity of neural circuits to influence mood, sleep and other aspects of behavior.

Scientists have known for several years about two vesicular glutamate

transporters, VGLUT1 and VGLUT2. As would be predicted, they are expressed on nerve cells that release glutamate. More recently, scientists have identified VGLUT3. To their surprise, they have discovered that VGLUT3 is expressed primarily by nerve cells that release GABA, serotonin and acetylcholine, another neurotransmitter. VGLUT3 is also released in some non-nerve cells, in tissues outside the brain. These findings led scientists to suspect that VGLUT3 might support some function other than neurotransmission.

In the current study, published in the Jan. 24, 2008 issue of “Neuron,” the team explored the role of VGLUT3 in mice genetically engineered to lack the transporter. The effect was dramatic.

“Mice lacking the transporter are completely deaf from birth,” says the senior author of the study, Robert Edwards, MD, professor of neurology and physiology at University of California, San Francisco. “Moreover, they had significant seizures.”

As the gene that encodes VGLUT3 is known to have sequence variations in humans, it is possible that these or other variations may be the underlying cause of deafness or epilepsy in humans, according to the researchers. They plan to screen people with these conditions for variations in the vglut3 gene, says the first author of the study, Rebecca Seal, PhD, a postdoctoral fellow in the Edwards laboratory

In addition, because the mice in the study lacked the protein in all cells that would normally make it, the team plans to make a “conditional knockout,” in which the gene is inactivated only in specific types of nerve cells. This will reveal which nerve cells expressing VGLUT3 account for a particular brain function.

At the outset of the study, the team knew that VGLUT3 was expressed during brain development by a population of inhibitory GABAergic

neurons in the brainstem pathway that transmits information about sound. They suspected that the absence of VGLUT3 -- which would allow the release of the excitatory glutamate -- might produce a subtle defect in sound localization. Instead, the animals were completely deaf.

The explanation, they learned, was that VGLUT3 contributes to the release of glutamate at a key point in the production of sound. It turns out that inner hair cells of the cochlea, which are known to convert the auditory input, or signal, into glutamate release, express VGLUT3, and the transporter contributes to the release of glutamate onto the first neuron in the pathway that carries sound into the brain. Without VGLUT3, no glutamate is released at that synapse.

The scientists also knew from the outset that VGLUT3 is expressed by a subset of neurons in the hippocampus and cortex that are known to release the inhibitory transmitter GABA. The presence of VGLUT3 suggested that these neurons might also release the excitatory glutamate. Since inhibitory neurons contribute to a range of oscillations in brain wave activity, the team hypothesized that disruption of these systems might affect brain wave activity in the cortex.

In fact, an EEG (electroencephalograph) revealed that all of the mice had seizures, and even when they weren't having full blown attacks they had abnormal electrical discharges in the brain, known as "epilepiform" activity. Surprisingly, the seizures -- which last up to two minutes -- were accompanied by little or no change in behavior.

The team plans to screen young patients with hereditary or early-onset epilepsy to see if they have mutations in this protein, says Edwards.

Since VGLUT3 may be required for relatively subtle aspects of behavior not easily elicited in a mouse, the researchers would also like to identify and study human patients, according to Edwards. The neuromodulatory

effect of glutamate release by serotonin neurons, he says, may be easier to detect in humans.

“If we found patients lacking VGLUT3,” he says, “we could carry out psychological testing, which would in turn give us an idea why most serotonin neurons also release glutamate.

“This is a case of a mouse model leading us to patients, who will, in turn, suggest additional functional roles for glutamate that we can test in the mouse. The results will help us to understand basic brain function and how it goes awry in disease.”

Source: University of California - San Francisco