'Chemical earmuffs' could prevent hearing loss

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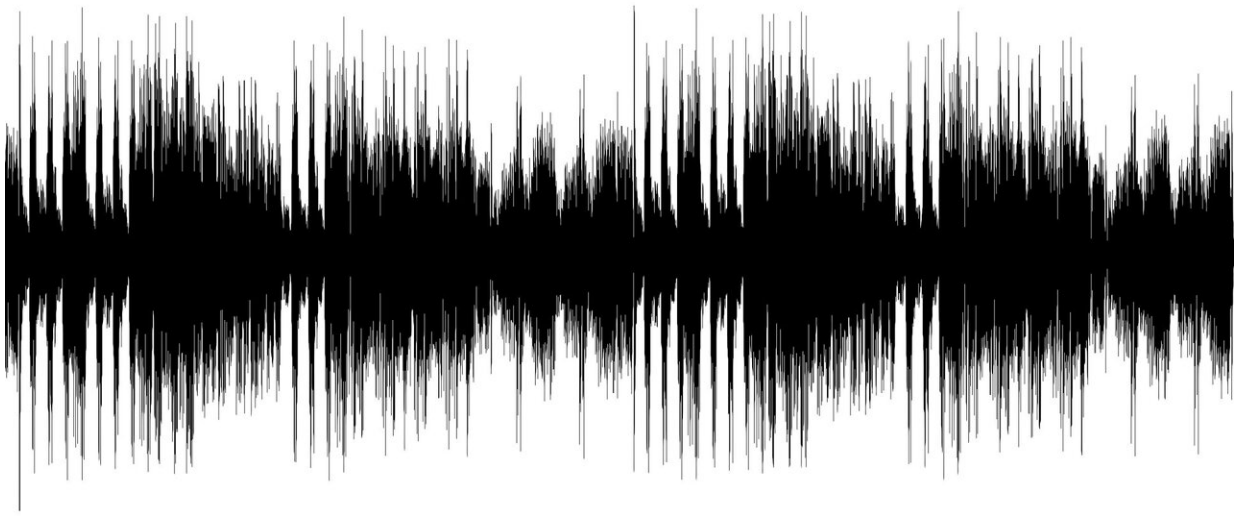

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Once you start to lose your hearing, you can't get it back. But what if you could prevent hearing loss by blocking in advance the effects of loud noises?

That's a route a team of biologists at the University of Iowa and Washington University, St. Louis, say may be possible after the researchers identified a receptor that, when blocked, can prevent a

common type of hearing loss.

Receptors are part of a suite of molecules on nerve cells in the ear that bridge the passage of sound and auditory information from inner-ear hair cells—the sound sensors—to the brain. The successful transmission of sound from hair cells to nerve cells, which occurs through a junction called a synapse, is integral to hearing in animals, including humans.

The researchers identified that some receptors involved in the hair-cell-to-nerve-cell transmission lack a protein called GluA2, and it is these receptors that are responsible for synaptopathy, or hearing loss caused by irreparable damage to the synapses.

The biologists employed a drug in mice that selectively blocked the GluA2-lacking receptors, and prevented the mice from experiencing synaptopathy when exposed to noise.

The approach was like outfitting the mice with chemical earmuffs that prevented them from sustaining hearing damage by blocking the breakdown that occurs in some synapses between inner ear hair cells and nerve cells when loud noises occur.

"It wasn't just putting earmuffs on—these earmuffs prevent the damage caused by loud sounds but don't muffle the sound," says Steven Green, professor in the Department of Biology and corresponding author on the study, published in the journal *Proceedings of the National Academy of Sciences*.

The experiments in mice indicate there is the potential to inject a drug that would prevent hearing damage in people before they're exposed to damaging noise. Conceivably, soldiers who are expected to encounter loud sounds in their duties could take a hearing-protection drug before exposure to those sounds, yet still hear commands. To be fair, this is

more conjecture than fact, although the U.S. Department of Defense helped fund the research.

"Permanent hearing damage can be caused by noise levels that have been considered 'safe,' and people need to be careful about noise exposure because we can't yet repair synapses or regenerate hair cells," Green says. "Our chemical earmuffs are, currently, just an indication of the direction research can go, not yet a proven, safe means of protection in humans."

In hearing, a chemical called glutamate is released from hair cells; this chemical transmits sound information at the synapse between inner-ear hair cells and nerve cells. However, loud sounds or even sustained moderate noise—such as sound coming through earbuds—cause the hair cells to release a glut of glutamate, effectively gumming the synaptic transmission of sound to brain neurons.

More specifically, it's the entry of calcium into the inner ear neurons through GluA2-lacking glutamate receptors that leads to synaptopathy. The researchers identified at the molecular-level receptors without GluA2, meaning those terminals that could cause hearing damage by allowing a flow of calcium. Even more, they then learned that if they blocked the receptors without GluA2, the GluA2-containing receptors picked up the slack, and hearing was maintained.

In the mice experiments, they showed a drug called IEM-1460 could target—and block—the receptors without GluA2.

"What we found is if you block the GluA2-lacking receptors, a.k.a. calcium-permeable receptors, then you can prevent the damage, and the mouse can hear just fine because it still has the GluA2-containing receptors that can mediate synaptic transmission," Green says. "Now, we have a drug that doesn't prevent hearing, but does prevent hearing

damage."

"For a long time, it has been assumed that cochlear synapses are not permeable to calcium, because all of the synapses have the GluA2 subunit," adds Mark Rutherford, assistant professor in the Department of Otolaryngology at Washington University and a co-author on the study. "We have found that cochlear synapses have both GluA2-lacking and GluA2-containing glutamate receptors, implying that some of them are indeed highly permeable to calcium. With high-resolution microscopy of cochlear synapses we have provided a mechanistic explanation for the protection of these synapses from noise exposure by the calcium-permeable glutamate receptor blocker IEM-1460."

In this study, IEM-1460 was introduced directly into the cochlea through a surgical procedure. Green hopes to find other drugs that could prevent hearing damage and that could be administered noninvasively.

More information: Ning Hu el al., "Protection of cochlear synapses from noise-induced excitotoxic trauma by blockade of Ca2+-permeable AMPA receptors," *PNAS* (2020). www.pnas.org/cgi/doi/10.1073/pnas.1914247117

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