Scientists find mechanism that causes noise-induced tinnitus and drug that can prevent it

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An epilepsy drug shows promise in an animal model at preventing tinnitus from developing after exposure to loud noise, according to a new study by researchers at the University of Pittsburgh School of Medicine. The findings, reported this week in the early online version of the *Proceedings of the National Academy of Sciences*, reveal for the first time the reason the chronic and sometimes debilitating condition occurs.

An estimated 5 to 15 percent of Americans hear whistling, clicking, roaring and other phantom sounds of tinnitus, which typically is induced by exposure to very loud noise, said senior investigator Thanos Tzounopoulos, Ph.D., associate professor and member of the auditory research group in the Department of Otolaryngology, Pitt School of Medicine.

"There is no cure for it, and current therapies such as hearing aids don't provide relief for many patients," he said. "We hope that by identifying the underlying cause, we can develop effective interventions."

The team focused on an area of the brain that is home to an important auditory center called the dorsal cochlear nucleus (DCN). From previous research in a mouse model, they knew that tinnitus is associated with hyperactivity of DCN cells—they fire impulses even when there is no actual sound to perceive. For the new experiments, they took a close look at the biophysical properties of tiny channels, called KCNQ channels, through which potassium ions travel in and out of the cell.

"We found that mice with tinnitus have hyperactive DCN cells because of a reduction in KCNQ potassium channel activity," Dr. Tzounopoulos said. "These KCNQ channels act as effective "brakes" that reduce excitability or activity of neuronal cells."

In the model, sedated mice are exposed in one ear to a 116-decibel sound, about the loudness of an ambulance siren, for 45 minutes, which was shown in previous work to lead to the development of tinnitus in 50 percent of exposed mice. Dr. Tzounopoulos and his team tested whether an FDA-approved epilepsy drug called retigabine, which specifically enhances KCNQ channel activity, could prevent the development of tinnitus. Thirty minutes into the noise exposure and twice daily for the next five days, half of the exposed group was given injections of retigabine.

Seven days after noise exposure, the team determined whether the mice had developed tinnitus by conducting startle experiments, in which a continuous, 70 dB tone is played for a period, then stopped briefly and then resumed before being interrupted with a much louder pulse. Mice with normal hearing perceive the gap in sounds and are aware something had changed, so they are less startled by the loud pulse than mice with tinnitus, which hear phantom noise that masks the moment of silence in between the background tones.

The researchers found that mice that were treated with retigabine immediately after noise exposure did not develop tinnitus. Consistent with previous studies, 50 percent of noise-exposed mice that were not treated with the drug exhibited behavioral signs of the condition.

"This is an important finding that links the biophysical properties of a potassium channel with the perception of a phantom sound," Dr. Tzounopoulos said. "Tinnitus is a channelopathy, and these KCNQ channels represent a novel target for developing drugs that block the

induction of tinnitus in humans."

The KCNQ family is comprised of five different subunits, four of which are sensitive to retigabine. He and his collaborators aim to develop a drug that is specific for the two KCNQ subunits involved in tinnitus to minimize the potential for side effects.

"Such a medication could be a very helpful preventive strategy for soldiers and other people who work in situations where exposure to very loud noise is likely," Dr. Tzounopoulos said. "It might also be useful for other conditions of phantom perceptions, such as pain in a limb that has been amputated."

More information: Pathogenic plasticity of Kv7.2/3 channel activity is essential for the induction of tinnitus, www.pnas.org/cgi/doi/10.1073/pnas.1302770110

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