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Tinnitus caused by too little inhibition of brain auditory circuits, study says

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Tinnitus, a relentless and often life-changing ringing in the ears known to disable soldiers exposed to blasts, unwary listeners of too-loud music and millions of others, is the result of under-inhibition of key neural pathways in the brain's auditory center, according to scientists at the University of Pittsburgh School of Medicine in this week's early online edition of the *Proceedings of the National Academy of Sciences*. The discovery, which used a new technique to image auditory circuits using slices of brain tissue in the lab, points the way to drug development and effective treatment for a condition that currently has no cure.

Prior research has shown that auditory circuits in the brain are more excitable in tinnitus sufferers, but until now it has not been clear whether that is due to hyperactivity of excitatory neural pathways, reduced activity of inhibitory ones, or a bit of both, explained senior investigator Thanos Tzounopoulos, Ph.D., assistant professor of otolaryngology and neurobiology, Pitt School of Medicine.

"This auditory imbalance leaves the patient hearing a constant ringing, buzzing or other irritating noise even when there is no actual sound," he said. "Tinnitus drowns out music, television, co-workers, friends and family, and it profoundly changes how the patient perceives and interacts with the world."

According to the American Tinnitus Association, tinnitus is the most common service-connected disability among veterans of the Iraq and Afghanistan conflicts. Of the 50 million who have experienced it, 16

million have symptoms severe enough to seek medical attention and 2 million tinnitus sufferers are unable to carry out day-to-day activities.

To identify what goes wrong in the brain's auditory circuits, Dr. Tzounopoulos' team created tinnitus in a mouse model. While the rodent was sedated, one ear was exposed to 45 minutes of 116 decibel (dB)-sound, equivalent to an ambulance siren. Intense noise exposure is thought to lead to damage in the cochlea, an inner ear structure critical to the neural transmission of sound waves, and clinically undetectable hearing loss.

Several weeks later, the scientists confirmed the exposed mice had tinnitus by conducting startle experiments in which a continuous, 70dB tone was played for a period, then stopped briefly and then resumed before being interrupted with a much louder pulse.

Mice with normal hearing could perceive the gap and, because they were aware something had changed, were less startled than mice with tinnitus, whose ear ringing masked the moment of silence in between the background tones.

The scientists then sought to determine what had gone wrong in the balance of excitation and inhibition of the auditory circuits in the affected mice. They established that an imaging technique called flavoprotein autofluorescence (FA) could be used to reveal tinnitus-related hyperactivity in slices of the brain. Experiments were performed in the dorsal cochlear nucleus (DCN), a specialized auditory brain center that is crucial in the triggering of tinnitus. FA imaging showed that the tinnitus group had, as expected, a greater response than the control group to electrical stimulation. Most importantly, despite local stimulation, DCN responses spread farther in the affected mice.

Dr. Tzounopoulos' new experimental approach has resolved why tinnitus-

affected auditory centers show increased responsiveness. After administering a variety of agents that block specific excitatory and inhibitory receptors and seeing how the brain center responded, his team determined that blocking an inhibitory pathway that produces GABA, an inhibitory neurotransmitter, enhanced the response in the region surrounding the DCN in the control brain slices more so than it did in the tinnitus slices.

"That means the DCN circuits are already 'disinhibited,' or blocked, in tinnitus," Dr. Tzounopoulos explained. "We couldn't block inhibition anymore to elevate the evoked response, like we could in the normal brain. And, when we blocked another inhibitory circuit mediated by the neurotransmitter glycine, or when we blocked excitatory pathways, there was no difference in the responses between the groups."

This means that agents that increase GABA-mediated inhibition might be effective treatments for tinnitus, he added. Dr. Tzounopoulos' team is now trying to identify such drugs.

Provided by University of Pittsburgh

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