

When silencing phantom noises is a matter of science

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Professor at the Karolinska Institutet, Sweden. Credit: Courtesy of frontiersin.org

With a clever approach, researchers point to the first gene that could be protective of tinnitus—that disturbing ringing in the ear many of us hear, when no sound is present.

Ringing in the ears or hearing of a sound inside one's head when no external sound is actually present is known as [tinnitus](#). It's a common problem that affects more than 1 person in every 10. While many learn to live with it, tinnitus can become much more than a minor ringing or buzzing sound. It can seriously disturb sleeping, concentration and daily living to the point of causing depression and anxiety.

"Our study in mice proposes the first gene related to tinnitus," says Christopher R. Cederroth, an assistant professor at Karolinska Institutet in Sweden. He and his team want to identify the molecules behind tinnitus, in an effort to find a treatment to silence the phantom noises. "We discovered that without normal function of the GLAST gene, animals are more prone to develop tinnitus," says Cederroth.

The gene codes for a glutamate transporter, a protein that works to take the [neurotransmitter glutamate](#) away from the synaptic space, where neural communication occurs, back into the cells. "Removing excess glutamate from the synapse is vital for healthy neural function, as uncontrolled glutamate levels outside neural cells overexcites neurons and has toxic effects," he explains. "Dysfunctions in [glutamate transporters](#) has been previously associated with seizures and [amyotrophic lateral sclerosis](#) and now, tinnitus."

The results, published in *Frontiers in Behavioral Neuroscience*, point beyond the known predominance of GLAST in the cerebral cortex and hippocampus, as its protective effects could happen in the ear. "Our study opens the possibility that higher expression of GLAST in the cochlea could create the resistance of mice to auditory insults, by preventing ototoxicity."

Since his first tinnitus studies in mice in 2009, Cederroth saw the need to improve the detection of tinnitus in this species, which offers facilitated behavioral and genetic manipulations for our understanding of the mechanisms behind the auditory disorder. "Curiously, mice appeared to be resistant to developing tinnitus," says Cederroth. "Only 20-50% of mice show behavioral changes that point to tinnitus after known risk factors, compared to 70-75% rats, for example." That posed a technical problem to scientists like Cederroth, who are looking for biological causes of the disturbance.

Testing behavioral detection of a sound gap, in different mouse strains, turned out to be their smart idea. "We found a solution that involved identifying the right mouse strain and the right stimulus timing. This improved the range of responses we could detect from animals with tinnitus in a mouse strain that is widely used in other field for genetic testing, giving the entire community a robust model for further testing of biological mechanisms of tinnitus."

This is a big step forward. Each mouse strain has a certain genetic background and shows a different level of baseline sensitivity to silent gaps. So modifying a certain gene in a sensitive strain and being able to observe a range of behavioral functions can point to the genes, and related molecules, that are required for specific types of tinnitus. "When the GLAST gene is knocked-out of mice on the C57 genetic background, the animals developed more tinnitus when exposed to salicylate, a derivative of aspirin known to be transiently toxic to ear cells."

Experimental models of tinnitus are normally made by exposing animals to loud noise or to drugs toxic to ear cells, such as salicylate, and then presenting animals with various behavioral tasks to measure their perception of non-existing sounds. One such behavioral test is GPIAS, which stands for gap pre-pulse of the acoustic startle reflex. The

principle behind this task is the normal and involuntary ability of animals to suppress a startle reflex in response to certain loud pulse, if the startling pulse is preceded by a silent gap in the background noise. "In a way, the pre-pulse gap normally serves to prepare the animal for the upcoming startling pulse, such that they startle less," explains the researcher.

"An animal that does not show this normal behavioral inhibition by the pre-pulse gap is showing a less efficient gap detection, in the form of a greater reflex response. This could happen when the animal perceives a phantom sound, interfering with the ability of sensing the gap properly—that is, like tinnitus," explains Cederroth. "As we change the frequency of the background noise to closely match an animal's ringing in the ear, the startle reflex is less efficiently suppressed by the pre-pulse gap."

Because of the improved sensitivity of the behavioral task in detecting tinnitus and clear candidate molecules, the GLAST deficiency model may very well serve to distinguish more subtle, yet unidentified mechanisms on how tinnitus is triggered and maintained. "We need to now investigate in more details what happens in the ear and in the brain to identify where GLAST is truly acting and how".

"There is a current need to standardize tinnitus diagnosis and how treatments are assessed, and our work points to the value of changing timing and frequency parameters to better diagnose cases using this methodology. These improvements will have to be tested in humans with tinnitus, as it is of outmost importance for drug discovery to have comparable read-outs between animal models and humans."

"A method that can objectively quantify a decrease in tinnitus perception after a given treatment would be a major break-through in the field," says Cederroth. "When coupled with human genetic studies, this

endeavor could ultimately improve the drug development process and lead to the preventive or curative treatment of tinnitus." The work is important to help such a large number of people, 70 million only in Europe and over 25 million in the US. "Tinnitus is a symptom, not a disease itself, as it can result from various potential causes, such as hearing loss due to damage of hair cells in the ear, head injury or infection, toxic drugs, psychiatric and neurodegenerative disorders or circulatory problems."

So, understanding tinnitus is a multi-disciplinary affair, and current knowledge is scattered, explains Cederroth. "This work is part of an effort to gather all the expertise to solve problems of heterogeneity, in how tinnitus becomes a problem to some but not all people and why they respond differently to treatments." By bringing together the global state of the art in tinnitus research, he hopes awareness will increase. "People with tinnitus need help that until now, we have not been very successful at providing."

More information: Hong Yu et al, GLAST Deficiency in Mice Exacerbates Gap Detection Deficits in a Model of Salicylate-Induced Tinnitus, *Frontiers in Behavioral Neuroscience* (2016). DOI: [10.3389/fnbeh.2016.00158](https://doi.org/10.3389/fnbeh.2016.00158)

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