

ATA-Funded Research Toward the Cure

Progress Report

The Glycine Receptor: A Possible Therapeutic Target for Tinnitus

*Donald Caspary, Ph.D., Southern Illinois University
School of Medicine*



Estimates are that 15 to 35 percent of the population of the United States experiences tinnitus, or phantom sounds, a subjective “ringing in the ears.” Up to 10 percent of these people consider their symptoms to be severe and disabling (Cooper, 1994). The incidence of tinnitus is likely increasing because of increased environmental noise exposure through headsets, for example, and because people in the U.S. are living longer than ever before.

One theory about what causes tinnitus is that the loss of normal sound input due to hearing loss leads to changes in the brain. These brain changes frequently involve a loss of normal inhibitory activity. This means that when hearing is lost, some brain chemical circuits malfunction. These circuits normally adjust the way that certain brain cells respond to sound. So when these inhibitory circuits malfunction, other nerve cells may show increased activity, known as hyperactivity. When this hyperactivity occurs, normal background sounds in the brain may become audible. Tinnitus researchers today are focusing their attention on this nerve cell hyperactivity as a likely cause of tinnitus generation.

During the first year of our study, rats were exposed to one hour of intense sound that was focused into one ear. Three months following this sound exposure, a group of older sound-exposed rats appeared more likely to develop tinnitus than were the younger sound-exposed animals. Both young and aged animals showed long-term changes to their inhibitory brain chemicals in one specific part of the brain: the dorsal cochlear

nucleus (DCN). These inhibitory brain chemicals help process sound signals in the DCN. Based on a number of recent studies, one recurring theory is that this sound processing system is compromised or altered in people or animals with tinnitus. This leads to increased nerve cell activity, which could lead to the appearance of tinnitus.

We examined the nature of one key inhibitory receptor, called the glycine receptor, in the circuits of the DCN. A decrease or change in the amount of auditory information (from sound) received by the DCN due to some kind of damage to the inner ear, may lead to a change in the makeup of this receptor. It could be that these changes in the makeup of the DCN are what lead to the hyperexcitability that causes tinnitus.

Our preliminary results show profound changes in the makeup of the glycine receptor in the DCN of young and aged animals with evidence of tinnitus, as opposed those without tinnitus. Young sound-exposed animals showed increased levels of a naturally occurring compound, called BDNF, that protects the nerves in the brain. This was especially interesting since young animals with marginal evidence of tinnitus had an increase of the protective BDNF, while old animals with strong evidence of tinnitus had no increase of this protective compound.

During the second year of the grant, we will focus on confirming these brain chemical changes. In addition, we will examine responses of brain cells recorded from the DCN of animals without tinnitus and of young and aged animals with evidence of tinnitus. It is the goal of these studies to compare brain chemical findings with the recordings from DCN brains cells in animals with and without evidence of tinnitus.

When we understand the relationship between the chemical changes and the physical changes that occur in the brain, we should be able to select the right drugs to test to relieve the impact of tinnitus. 📌

Interview with ATA-Funded Researcher Donald Caspary, Ph.D.

ATA: Dr. Caspary, what led you to become a tinnitus researcher?

DC: My interest in tinnitus, which developed over the last seven or eight years, began when tinnitus researchers Carol Bauer and Tom Brozoski joined our faculty at Southern Illinois University. Their laboratory is directly across the hall from mine, which greatly helped our day-to-day interactions. But I'd already had a long-standing interest in topics related to tinnitus, particularly about how the dorsal cochlear nucleus (DCN) works. The DCN is a very small part of the brain related to hearing. With my interest in the DCN, and their being right next door, well, it was an inevitable collaboration with Tom and Carol.

Up to that point, I had been concentrating solely on age-related changes of certain brain chemicals, called neurotransmitters, in the central auditory pathway. This is the pathway that carries a sound signal from the ear to the part of the brain that interprets sound. It was apparent to me from these studies that aging impacts the ability of our brains to process sound.

ATA: Are there brain chemicals related specifically to tinnitus?

DC: Possibly yes. "Inhibitory" chemicals in the brain normally allow brain cells to faithfully reproduce the rapid changes in sounds that occur in speech. They do this by preventing hyperactivity. In our DCN experiments, we found that the normal inhibition wasn't working at several sites along the central auditory pathway. In these areas, the brain cells appeared to be just the opposite – that is, hyperactive. We also learned that in older brains, the age-related hyperactivity was similar to the hyperactivity that follows excessively loud noise exposure.

Together, Dr. Bauer, Dr. Brozoski, and I found that brain cell activity recorded from animals with tinnitus had an increased response to sound. These findings suggested a loss of inhibitory function of the brain chemical *glycine*. After that discovery, we studied rats whose behavior showed that they had tinnitus, and then examined their sensitivity to this same brain chemical.

ATA: The dorsal cochlear nucleus (DCN) has been the subject of many tinnitus research studies recently. How close are we to understanding enough about this brain structure to move tinnitus research to the next level – that is, developing a drug to quiet tinnitus?

DC: My laboratory and other labs have been studying the DCN for many years. We've now gathered a large amount of data about this structure, and continue to examine DCN changes in the context of tinnitus. We need to better understand how the DCN changes when input from the ear is reduced.

Within the last year, we've developed a new and perhaps more efficient way of assessing if animals have tinnitus. We're very excited about that. This new method uses specific drugs to determine if the animals have tinnitus. This should enhance our ability to screen potential new medicines to treat tinnitus. We're also currently exploring a number of ways to determine if there are brain chemical changes in animals with behavioral evidence of tinnitus.

ATA: Do you see your work carrying over into real therapies for people?

DC: The most exciting thing that could happen for me as a researcher is to have an impact on the quality of life of people suffering from tinnitus. I have been working on central auditory problems for my entire research life. It seems highly likely that if we can figure out the neurochemical changes that underpin the development of tinnitus, we should be able to make intelligent drug selections for the treatment or elimination of tinnitus. It is this possibility that has made the study of tinnitus most exciting for me. 🍷

Dr. Caspary is a professor and Assistant Dean for Faculty Development at Southern Illinois University School of Medicine, and a member of ATA's Scientific Advisory Committee. His research project was recently funded by ATA.