Conversations in Tinnitus

with Susan Shore, PhD

Topic: Breakthrough Using Multisensory Stimulation to Reduce Tinnitus

Transcription:

S1 00:00 Welcome to *Conversations in Tinnitus*, a podcast of the American Tinnitus Association. The American Tinnitus Association is a nonprofit organization dedicated to research, advocacy, education, and support for people who live with tinnitus. *Conversations in Tinnitus* podcasts are an extension of ATA's magazine, *Tinnitus Today*, the only publication dedicated to educating the public and practitioners about ongoing research, treatments, and management of the condition. [music]

S1 00:48 And thank you for joining us for another episode of *Conversations in Tinnitus*. I'm John Coverstone, along with my co-host, Dean Flyger. And joining us for this episode is Dr. Susan Shore, who is a professor at the Kresge Hearing Research Institute at the University of Michigan. So, thanks for joining us, Dr. Shore.

S2 01:08 You're very welcome.

S1 01:09 And we had you on because you came out with some wonderful research – amazing research – that was published back in January. I know this got a lot of public attention, so probably many of our listeners and ATA members have already read your research. But to talk to you more about it, you did some work with both guinea pigs and humans, looking at bimodal stimulation. So that's using two modes of stimulation to treat the tinnitus and have some positive effects. So, I'm just going to let you start by telling us what you did in the research and the outcomes that you found and how that's continuing.

S2 01:49 Okay. Well, I'll try to be as clear as I can. But please stop me if I get too technical. So, we've been looking at an area of the brain called the cochlear nucleus for about two decades now and studying how particular neurons within this cochlear nucleus respond to sound and what happens to these neurons when we overexpose guinea pigs to loud sound, such as humans would experience, that generate tinnitus. And what we discovered was that when we exposed these animals to loud sound; it doesn't even have to be hugely loud. It can be just as loud as sounds that cause what we call hidden hearing loss, so hearing loss that has a temporary threshold shift. We can produce tinnitus in animals with those kinds of sounds. And we find that about half the guinea pigs get tinnitus. Now, this is important because we can then compare the brains of the guinea pigs that get tinnitus with the brains of the guinea pigs that don't get tinnitus. And we can learn a lot about how tinnitus is generated by doing that. So, what we discovered is that in the guinea pigs that get tinnitus, the firing rates of these fusiform cells in the dorsal cochlear nucleus increase. So, the spontaneous firing rate that's there all the time, even when you don't have a sound there, spontaneous firing rate varies. But after this noise exposure and after we measure at the behavioral evidence of tinnitus in these guinea pigs, the spontaneous firing rates increase. And what's more, the neurons in that region, they synchronize with each other. And only the neurons in the noise exposure frequency region synchronize their firing. So, this could serve as a code for tinnitus in that specific frequency, specific neurons are now firing together, and they're sending the signal up to the rest of the brain.

S2 03:45 Another thing that we discovered that was important for what led to the treatment that we published was that we discovered that these particular fusiform cells not only receive input from the cochlea to stimulate them, but they also receive input from non-auditory regions of the brain. And these regions of the brain are regions that respond to touch. So, they're called somatosensory neuron. And then we discovered in many of our studies over these many years that when we stimulated these neurons with sound, combined with somatosensory stimulation. There were certain combinations of somatosensory and sound stimulation that could increase the firing rate of these neurons for long term. So, it would cause long-term plasticity. But we also found that when we changed and reversed the order and the intervals of these sounds and the electrical stimulation that we could depress the neurons. We could cause long-term depression, often called the LTP. And so we spent a long time figuring out which particular combinations of somatosensory and auditory stimulation could produce this long-term depression. And then we based our treatment on that. And so what we ended up is the combination of sound and electrical stimulation was that that we had shown in the guinea pigs caused this long-term depression of these neurons. And then when we treated guinea pigs with those sounds repeated every day for 30 minutes, we were able to reduce the tendencies in the guinea pigs. And it was those particular sounds that we then took into our human study and tried those on the human.

S1 05:26 And in that process, as I remember, you also were very careful to look at what affected the guinea pigs negatively, as well as what affected them positively. So, you didn't carry that over to humans, correct? There some really good controls in your study.

S2 05:41 Right. Exactly. Well, we thought it was very important to do that and look at the actual brain to see what happened to them when we used different kinds of stimulation. So, for example, if we used somatosensory stimulation alone, we found that we got more LTPs, so the long-term potentiation, increasing the firing rate of the neuron, then long-term depression. And we predicted that that might make the tinnitus in the guinea pigs worse. And in some cases, it did make the tinnitus worse in the guinea pigs, and so we didn't use that in the human. And also, we reversed. We tried, in our previous experiments to use different orders and intervals of sounds. And the ones that caused LTP, were also excluded because we didn't want to increase the tinnitus in humans.

S1 06:32 And I mentioned that. I brought that up because we were talking a little bit, before we started recording, about some of the methodology of your research and how careful you are. And we agreed that that was something important to talk about a little bit because you have spent years developing this paradigm to use. And you talked a little bit about some of the previous studies that have been done to gradually kind of hone in – if I can use that term – on what had the best opportunity or the best promise to have effective results. So, this wasn't something to where you said, "Hmm, we've been doing acoustic simulation, and we've been doing electrical stimulation. Hey, let's put them together." It wasn't sitting around the table deciding that this is what you're going to try to do. This comes out of years of painstaking research.

S2 07:17 Right. And I think one of the important things that we discovered was that the combination of signals that we used produced different effects in animals that had tinnitus versus animals that weren't noise-exposed. And then that was actually crucial for us because these so-called timing rules, which signals produce which effects in the neurons, is completely opposite in animals that get tinnitus. And that's because the circuitry has changed in these neurons. And so if you just do some stimulation in a normal animal, and then you take those results, and you move that into humans, that could lead to some deleterious effect because you've been looking at the wrong brain

in your research. You need to look at the tinnitus brain and not a normal brain. So that was a very important pivotal point for us when we discovered that all of these timing rules changed when we induced tinnitus in the animals and we had behavioral evidence of that tinnitus.

S1 08:15 And what were you looking at for behavioral evidence? This has come up a couple of times for us in the last year of our podcasts. And so I'm curious to get your insights as someone who's done many years of research in this area, how you're looking at that.

S2 08:28 Yeah. Well, this is a controversial issue. And for a long time, many labs have been using a technique called gap-induced suppression of the acoustic startle response in which a loud sound makes the guinea pig, or the rat, or the mouse startle, and you have a background noise before you have the startle stimulus. But then when you place a gap in the background sound, it's almost like that's a warning to the animal that the loud sound is going to occur, and this reduces the startle amplitude. That effect has been shown for many, many years. It's a known effect. The controversy came up because some labs didn't get good results with their gap detection procedures. And so other labs have now sort of gone into using the gap detection in a much more careful manner and induced some controls that ensure the effectiveness and the reproducibility of these techniques. One of the things that our lab has done is that we, for example, we make sure that our animal doesn't have a permanent hearing loss because if the animal has hearing loss, then they wouldn't be able to hear that gap, and then that wouldn't be able to suppress the startle. And so you would get an erroneous readout on that.

S2 09:47 So that's one of the reasons why we use a temporary threshold shift model. The other thing that can happen when you use startle responses is that the startle responses themselves can adapt. So, if you test your animals too often, you get a much smaller startle response, and then there's less startle to decrease. And so that's another place where you can get a lot of error in the readout of the technique. The third thing that we've done is we've adapted the procedure that was developed by Alan Palmer's lab in the U.K. to use a guinea pig's ear twitch instead of a whole-body startle, which enables us to get a much more reliable startle from time to time, from each presentation. And also, it enables us to use a much lower sound pressure level to elicit the startle. So those are some of the things that if you're going to use this technique, you need to be very careful about because otherwise your readout is going to be erroneous. And then in addition, now there are several labs who are combining operant conditioning, which has its own set of problems because it takes much longer to do. You have to train the animals, and there can be some extinction involved in those techniques. But our lab and other labs now also using that – not all the time – but to check the gap detection procedure. And there's also coming out, at least in our lab and then a couple of other people that I've talked to, in that, we're identifying the same animals that have tinnitus with both techniques. So, I think as long as these control measures are in place that this technique can be a good technique, at least in guinea pigs. So, I can't really speak for other species because that's not what we're using.

S1 11:30 Sure. That makes sense. Absolutely. And that also makes me wonder. Let me actually get some background to what I'm thinking here. This goes all the way back to some of the other podcasts that we've had back – what I'm thinking of is our conversation with Jinsheng Zhang, who we had on last year. And we talked a lot about neuroanatomy with him, and maladaptive plasticity, and many of those fundamental things that you're dealing with on a daily basis. But are there ways that you can be sure that you are creating tinnitus in the – I believe you said dorsal cochlear nucleus – he mentioned dorsal lateral cochlear nucleus? For our listeners, the cochlear nucleus is really kind of the first stop in the brainstem, the nerve

that carries the information from the ear up to the brainstem, actually connects with the cochlear nucleus. So that's a very important structure in hearing. Yeah. But--

S2 12:22 Yeah. Jinsheng Zhang would have been talking about the dorsal cochlear nucleus.

S1 12:27 And so do you have ways of inducing tinnitus where you know specifically that it's going to occur in that area? Because we're also seeing research of tinnitus may have multiple sites of generation. Or maybe you have some thoughts on that too, so.

S2 12:37 Oh, yeah. I'm sure it has multiple sites of generation. But the first place that the signal goes into in the brain is the dorsal cochlear nucleus. So, if you get net auditory nerve input going to the brain, the first place that's going to see that is the dorsal cochlear nucleus, and even the ventral cochlear nucleus, which we haven't talked much about, but we're looking at that nucleus as well. So, some of the neuro-plastic changes that happen occur because of a reduced auditory nerve input into the brain. And so the first place to look at that is in the cells of the cochlear nucleus. Whatever happens to the cells of the cochlear nucleus, that's then going to get transmitted to other parts of the brain, for example the inferior colliculus and also the thalamus. Now, there've been people who looked for correlate tinnitus in both of those places, in the thalamus, the medial geniculate nucleus, and also in the inferior colliculus. And in both of those places, a hyperactivity has been described. But the hyperactivity that's seen in the thalamus seems to be a little bit more reliably connected with tinnitus than the hyperactivity that's seen in the inferior colliculus. There've been a few studies in the inferior colliculus that have shown the hyperactivity in response to noise damage. But some studies suggest that that is not really connected with tinnitus, but it's rather the results of the noise damage per se. So, the studies in the thalamus that have been done by Don Castoria and his team have shown tinnitus specific effects in that animals with tinnitus show increased synchrony and increased spontaneous firing rate than animals without tinnitus do not. And, so, if you get a nucleus that shows increase in spontaneous activity after noise damage but is not different between animals with and without tinnitus, then you would say that that's not a tinnitus specific correlate. So, it is possible that the signal – the hyperactive signal – is transmitted directly from the cochlear nucleus to the thalamus, bypassing the inferior colliculus. But no one has really examined that yet. And I mean, there's still a huge amount of research that needs to be done …

S1 15:00 Sure. Sure.

S2 15:01 … if the signal has to reach the auditory cortex where it would be interpreted.

S1 15:05 So, what I'm getting from that is we may be looking at some of the effects of the tinnitus rather than the cause. And, of course, we want to try to zero in on the cause as much as possible if we're treating.

S2 15:18 Well, I think we can say that it's hard to say cause, but I think that our studies have shown that if we look at the auditory nerve, so we look at the synapse counts within the cochlea (and we work in collaborating with Charlie Liberman for that), what that has shown is that without temporary threshold shift model, we get a synapse loss – the synapse between the inner hair cells and the auditory nerve – we get a synapse loss for both the animals with and without tinnitus. So, there is a little bit of synapse loss, but there's no difference between the synapse loss between the animals with tinnitus and without tinnitus. Then when we get into the fusiform cells, we see a huge difference between the animals with and without tinnitus. So, one could say that whatever causes those fusiform cells to be hyperactive in just the tinnitus animals is what's causing the tinnitus. And that isn't going to be one thing. It's going to be a number of factors that make the circuit change in a way that the circuit becomes hyper-excitable. Some of those factors are increase in somatosensory innervation from somatosensory centers into the cochlear nucleus. And we've shown that to be

true. That's one factor that could increase the firing rate of these neurons because the input that comes in from the somatosensory systems is glutamatergic, and it's excitatory.

S1 16:48 And then accompanying that, there are a lot of changes that happen because of homeostatic plasticity because of the reduced auditory nerve input into the brain. It's like the brain is crying out saying, "Give me more glutamate." And so it sends a signal to draw in more glutamate from other places, for example, the somatosensory system. And then in response to that, there are receptors changes, ion channel changes, many changes that happen, some of which are known, and some of which are not yet known.

S2 17:19 And the somatosensory system – I can talk – is essentially our sensory system for touch and our awareness of physical contact. So, let's bring this back to humans a little bit because you mentioned that in your opening discussion. And then we kind of got away on this other research-based stuff, which is great. But you did bring this into humans after you had seen success with the guinea pigs. And you had some positive results with humans. Of course, this is fairly early in this. So, I'm sure there's still a lot of things you want to look at, a lot of refinement and additional paradigms and having longer lasting effects, things like that. But where are we right now in using this kind of stimulation with humans? And what kind of promise is this showing even now, which is well after I'm sure you actually concluded this part of the study?

S1 18:16 Okay. Well, we're in the process of starting another trial that will begin in the fall. And this is funded by the NIH BRAIN Initiative. So, we're already recruiting subjects for the study. And this is going to be a replication of the first study with some refinements. So we're going to be treating the people for longer, for instance. And the reason for that is that if you look at the results that we got from the trial, we saw cumulative decrease in tinnitus loudness and a cumulative decrease in TFI scores, which is the life impact of this treatment, over four weeks of the treatment. And because it was cumulative – the improving – the next thing to do is to treat for a little bit longer to see whether that continues to accumulate. And then it lasts longer than it did in the first trial. So that's one of the things that we've already established that we're going to be doing. And then as the study goes along there could be other things that we treat as well.

S3 19:24 So, if we're trying to translate this to clinical practice, which John and I are interested in ultimately, how far away do you think we are to see some of your results to actually be useful for us?

S2 19:39 Well, it depends on how the trial – the outcome of the next trial is. And hopefully, by the end of next year, we will have that trial tied up, or we'll at least have a very good idea of how the trial has worked out. And then depending on that, then there would be commercialization efforts to move this to the clinic.

S3 20:02 Excellent. Thank you.

S1 20:03 Wow. That's seems to me kind of quick [laughter]. Now, that doesn't seem to you like it's quick because you--

S2 20:06 [crosstalk] by the end of next year. But I'm saying that's when these efforts would begin. I wouldn't want to promise anything sooner than it might happen.

S1 20:16 No. And anybody who's--

S2 20:17 So, it all depends on the science and the outcome of that science.

S1 20:21 Right. Right. And anybody who's been through the FDA approval process knows that's it's anything but quick.

S2 20:26 Exactly.

S1 20:27 But it may seem quick to us. But of course, you've been doing this for – what did you say – 15 years, this line of research in some form or other, so not quick for you. But it's got to be great to see those years of research cumulating in something that's showing promise. And now, you're doing a larger study, and refining methods, and may, within a year or so, be able to start making the journey into clinical practice. That's just got to be very rewarding. And I'd like to say on behalf of myself, and I'm sure many other millions of people, we really appreciate all those years that you've spent in the lab working on this to bring it this far.

S2 21:06 Right. Well, we hope it's got a lot farther to go than it's already come.

S1 21:10 Right. Right. Absolutely. What other research are you working on right now? Is this where you're really spending your time? Or do you have some other things that you're looking at as well in the tinnitus world?

S2 21:21 Well, we have another line of research that doesn't even have to do with tinnitus. And that is looking at synaptopathy, or hidden hearing loss, being a big topic in recent years. This is the kind of hearing loss that you might get after a rock concert where your ears feel muffled. And then after a couple days, you think that your hearing has gone back to normal. But this there's been a lot of work now out of the Harvard lab in particular, and a lot of other labs are now working on this, showing that even though your clinical audiogram looks normal, your hearing isn't normal. And you have a lot of trouble hearing in a bar when you go into a bar and there are other people speaking or any kind of other noisy background. And some of this has been postulated to be due to the synaptopathy that happens in the cochlea. So, what we're interested in looking at is what happens to the brain after cochlear synaptopathy. And so we're hoping to get some funding to – well, we've already received some funding. And we're hoping to get more funding to look at this in a lot of detail in the cochlear nucleus and other parts of the brain.

S1 22:33 Yeah. That's great.

S3 22:33 Excellent. That's exciting.

S2 22:35 Yeah. So hopefully, this will help us to understand a little bit better how humans and animals pull signals out of noise, and what things are broken down after synaptopathy, and then maybe how we would be able to restore that.

S1 22:53 Sure. Absolutely.

S3 22:53 Excellent.

S1 22:54 And this is actually something we are – not directly – but we are measuring somewhat in the clinic. Many of us are starting to do some measures. And we believe this is the underlying reason why certain conditions exist, certain difficulties exist, such as understanding speech in the presence of background noise without significant hearing loss, things like that. And we are actually measuring it in the clinic. But it will be nice when the research gives us a little firmer connection to what we're doing and maybe even leads to some different treatment methods so that we can address the problem more directly. But that's exciting that you're working on that. Well, I do want to thank you for joining us. And once again, we've been talking with Dr. Susan Shore, who is a professor at the Kresge Hearing Research Institute at University of Michigan. I'm John Coverstone, with me is Dean Flyger. And thanks again for joining us on *Conversations in Tinnitus*.

S2 23:48 You're welcome. It was lovely talking to you. [music]

S1 24:05 The American Tinnitus Association is a nonprofit organization dedicated to research, advocacy, education, and support for people who live with tinnitus. Gifts and donations to ATA are used to support research for a cure and other critical missions described on our website at www.ATA.org.