Tinnitus research advancements show a glimpse of the potential growing role for audiologists as key elements in the treatment of individuals with hearing loss and tinnitus.
ubjective tinnitus, a phantom auditory sensation occurring in the absence of a “real” sound can be a debilitating condition that negatively impacts quality of life, concentration, communication, and sleep. Although this condition has been documented as early as 1650 BC by the Egyptians, the lack of a biological mechanism provides a major obstacle for treatment. Tinnitus may be referred to as a condition rather than a disorder because it is a symptom that may be generated by a number of different pathologies. One such pathology is hearing loss; while the majority of people with hearing loss don’t develop debilitating tinnitus (a larger number develop tinnitus but not disabling tinnitus), most patients with tinnitus have hearing loss (>80 percent). Further, most people experience transient tinnitus after brief intense sound exposure or prolonged loud noise exposure, suggesting that hearing loss is strongly associated with the development of tinnitus.

One of the major advances in tinnitus research was the development of animal models over the last 20 years. Following the pioneering work of Dr. Pawel Jastreboff, a number of labs have demonstrated that animals exposed to conditions that induce tinnitus in humans behave during quiet conditions as if a real sound were present. The development of these animal models has led to the acceptance that, indeed, tinnitus is a biological phenomenon that can be documented in other species. This has resulted in opportunities to investigate the underlying mechanisms of tinnitus from hearing loss and other traumatic events that damage the ear or, more recently, the brain and ear after blast trauma similar to those observed in military personnel exposed to improvised explosive devices (IED). Based on data across a number of laboratories, there is strong evidence that hearing loss in both animals and humans can lead to persistent tinnitus. Imaging studies in both animals and humans have also shown that the manifestation of the tinnitus experience occurs not in the ear but in the brain.

While the animal and human data appear to correlate well, a new controversy has emerged more recently between two alternative approaches to tinnitus and tinnitus treatment. The first approach is that the primary cause of tinnitus distress is a chronic sound that cannot be escaped. Therefore, attempts to reduce the sound through pharmacological treatment, direct brain stimulation, transcranial magnetic stimulation, or sound therapy are the most logical approaches in reducing disabling tinnitus. In contrast, there is a strong countermovement that focuses primarily on the emotional response to tinnitus where the actual acoustic properties of the tinnitus become much less relevant. For instance, tinnitus retraining therapy (TRT), developed by Pawel Jastreboff, is a deconditioning paradigm designed to reduce the abnormal response to the phantom sound of tinnitus regardless of what the tinnitus sounds like. Similarly, cognitive behavioral therapy (CBT) aims to reduce the impact of the distress associated with tinnitus. In a recent presentation at the American Academy of Audiology’s AudiologyNOW! conference and exhibition (2010), it appears that the U.S. Department of Veteran’s Affairs (VA), which spent about $1 billion last year in tinnitus-related compensation, is beginning to accept this approach to treat the large number of veterans with tinnitus. It can be argued, however, that attenuating the response to tinnitus does not fully address the underlying problem, an incessant phantom perception of sound.

There is a strong incentive to embrace the approach that focuses on emotional response to tinnitus. First, one therapy fits nearly all tinnitus patients. Second, therapies can be implemented by audiologists, the primary healthcare providers for hearing loss. Third, the therapy is relatively low risk, and fourth, clinical trials have failed to identify drug therapies that could provide immediate tinnitus relief. However, a number of these trials showed a strong placebo effect, had inconsistent tinnitus measures, and did not have well-defined subject selection.

Conversely, there is some anecdotal and direct evidence that some pharmacological treatments may work in some subjects. In one study, Dr. Robert Levine showed that carbamazepine (tegretol) could suppress a subtype of tinnitus known as typewriter tinnitus. Additionally, there is some evidence from animal and human studies by Dr. Carol Bauer and Dr. Thomas Brozoski that pharmacological treatment with gabapentin can partially attenuate tinnitus.

Over the last eight years at the University at Buffalo, we have focused on the acoustic characteristics of tinnitus in both animals and humans. This work evolved from the human imaging studies by Dr. Richard Salvi and
Dr. Allan Lockwood. These studies showed that individuals with chronic tinnitus had different activation patterns to sound evidenced by PET imaging studies and that modulation of tinnitus in a subset of the test subjects via oral facial maneuvers changed the activation pattern correlated with tinnitus.

Most of our recent work has focused on tinnitus in animals exposed to unilateral noise trauma. Although this hearing loss model does not account for all tinnitus, it covers one of the sub-types of tinnitus most likely to be seen by audiologists. Our two animal models have somewhat similar characteristics to others reported in the literature. The first model we used was schedule-induced polydipsia avoidance conditioning (SIPAC). Under SIPAC, animals are placed under a schedule that induces large volumes of drinking driven by intermittent food pellet delivery. Interestingly, animals do not need to be water deprived for this paradigm to work; however, they are food restricted to 85 percent of their free-feeding weight (i.e., they are hungry).

During the first phase, we present intervals of sound (4 kHz narrow band noise) and quiet throughout the session. Animals drink throughout the session in bursts following automatic food delivery (food is delivered one pellet per minute automatically without any need for the animal to respond). Next we begin to slowly introduce a brief foot shock (two to three sec) if the animals drink during a sound interval, but no shock is delivered if the animals drink during quiet.

The animals quickly learn to only drink during quiet. Next, we vary the intensity (40–60 dB SPL) and frequency (4–20 kHz) of the narrow band noise (shock is delivered if animals drink in the presence of any of the sound trials). It typically takes one day for animals to generalize and refrain from drinking in the presence of any sound. In the first set of experiments we successfully replicated Jastreboff’s early results using sodium salicylate (main ingredient in aspirin) and quinine (an antimalarial agent). Both of these drugs also induce tinnitus in humans at high doses.

When treated with either of these drugs at high doses, rats refrained from drinking during the quiet condition and only ate the food pellets. After the session, animals would immediately start drinking when placed back in their home cage. These results suggested that animals perceived a phantom sound during the quiet condition (i.e., no external sound) and withheld their drinking during quiet intervals.

In a follow-up study using PET imaging in rats, we showed that high doses of sodium salicylate (250 mg/kg) shown to have behavioral evidence of tinnitus in SIPAC showed activity patterns that were significantly higher than activity patterns in quiet and were similar to patterns evoked by real sound in the inferior collicullus and auditory cortex. In contrast, in animals with hearing loss but not tinnitus, activity decreased in these same regions. (The study was funded by a generous grant from the American Tinnitus Association.)

More recently, we developed gap prepulse inhibition of the acoustic startle (GPIAS), as a screening tool for noise-induced tinnitus (by our colleague Dr. Jeremy Turner). An initial experiment correlated the effects of sodium salicylate under SIPAC with the effects on GPIAS cross-validating both measures in the same animals. Under GPIAS, an interval of continuous sound (noise or tone) is followed by a loud startling stimulus (broadband noise –105–115 dB SPL).

In rats, this sequences of events generates a large motoric startle response. However, if a brief silent gap (25–150 msec) is inserted into the continuous sound 0–100 msec before the startle response, the startle response is significantly reduced as the gap provides a salient cue of the imminent startle sound. We developed our GPIAS model so that we could test across a range of narrow band noise frequencies (6, 12, 16, 20, and 24 kHz). In our first experiments with GPIAS we showed that a high dose of sodium salicylate (250 mg/kg) resulted in poor GPIAS at 12–16 kHz but normal GPIAS at 6, 20, and 24 kHz. These results showed that animals could not reliably detect gaps at 12–16 kHz; results consistent with tinnitus in that frequency region (i.e., the tinnitus was filling the silent gap).

Interestingly, other laboratories using different animal models report evidence of tinnitus near these frequencies. Although sodium salicylate is a reliable inducer of tinnitus, it is not a clinical problem (or at least it is easy to solve by reducing the sodium salicylate dose). We hypothesized that by using unilateral noise trauma, we could induce hearing loss and tinnitus in one ear and leave the other ear functional to detect the carrier sound and startle sound under GPIAS. We had previously obtained data from SIPAC showing that unilateral noise trauma yielded decreased licking during quiet, suggesting the presence of tinnitus.

After a number of preliminary experiments, we discovered a number of interesting things about trying to produce noise-induced tinnitus in rats. First, the rat ear is relatively tough. We needed to expose rats to noise over 120 dB SPL for at least one hour to even induce measurable hearing loss by DPOAE. Second, a number of these animals with known hearing loss from DPOAE measures
in the exposed ear continued to perform the GPIAS with no deficit. Only in a subset of animals (~30–40 percent) did we find a reduction in GPIAS. Interestingly, the frequency of the GPIAS deficit was consistent with the hearing loss in the exposed ear (note other ear was normal under DPOAE). Our noise exposure parameters were 126 dB SPL of a narrow band noise centered at 16 kHz. We consistently showed deficits in GPIAS in the 16–20 kHz region. These results mirror human data where the tinnitus is in the region of the maximal hearing loss or in the transition zone from normal to impaired hearing.

Equipped with both these models we have performed a number of studies to look at drug treatments for tinnitus. While some traditional compounds such as the benzodiazapine anxyolitic, alprazolam, and the anticholinergic scopolamine, as well as numerous other drugs from different classes, failed to reduce evidence of tinnitus, we recently published on the effects of two potassium channel modulators, Maxipost and R-Maxipost.

Potassium channel modulators are interesting because potassium channels are expressed in the central auditory pathway. In our experiments, both these drugs suppressed sodium salicylate-induced tinnitus. More recently we tested the effects of Maxipost and R-Maxipost on noise-induced tinnitus. Here we found more modest results suggesting that both modes of tinnitus may have different underlying mechanisms.

This past summer, we hosted and presented exciting new results at the Fifth International Tinnitus Research Initiative Conference in Grand Island, New York. In collaboration with the Tinnitus Research Initiative and based on preliminary human data, we showed that the widely prescribed muscle relaxant cyclobenzaprine reduced evidence of single sided noise-induced tinnitus under GPIAS. These results were exciting because tinnitus was observed in the region of poorer hearing in the exposed ear, and a single cyclobenzaprine treatment suppressed the tinnitus for 24–48 h. This study suggests that there may be drugs in the market already that could be useful in treating tinnitus. It also opens the possibility that some natural supplements could help reduce tinnitus, although evidence of this thus far has not been overly encouraging.

While our recent efforts have focused on pharmacological treatment, there is growing evidence from the work of Dr. Jos Eggermont suggesting that sound enrichment prevents abnormal brain reorganization following noise trauma. In the human literature, it is known that sound therapy can be a useful and effective tool to manage tinnitus, but the underlying mechanisms as to how and where this occurs in the brain are not well understood. We have planned a series of preliminary experiments using our animal models to explore the potential role of sound therapy and how this mode of treatment reduces tinnitus. We have already shown that noise-induced and blast-induced hearing loss correlated with tinnitus reduces brain function evidence by impaired hippocampal neurogenesis.

Interestingly, impaired hippocampal neurogenesis has been associated with depression, opening the possibility of tinnitus animal models being used for more than the percept of tinnitus. Further, it opens the possibility that stress factors could be modulated to increase the probability of inducing tinnitus in animals. Stress is strongly associated with tinnitus distress, and animal models could elucidate the physiological mechanisms underlying the relationship of stress and tinnitus.

The original tinnitus experiments in Buffalo were performed in humans using imaging technology. The evidence garnered from these studies inspired the development of animal models to better understand the mechanisms underlying tinnitus. Over the last eight years we have moved between the animal realm and human realm with studies looking at mechanisms and therapy. This team approach was led by auditory scientists and audiologists working in conjunction with professionals from other disciplines. The advancements made show a glimpse of the potential growing role for audiologists as key elements in the treatment of individuals with hearing loss and tinnitus. We ought not to retract from the challenges of working with patients with tinnitus but, rather, embrace the opportunities available to them today and in the near future.

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