● **PERSPECTIVE**

# Current view of neurotransmitter changes underlying tinnitus

Tinnitus is the perception of a monotonous sound not present in the environment. Nearly 20% of the U.S. population suffers from tinnitus, and tinnitus has been reported to be the most prevalent service-connected disability of all U.S. veterans (Henry et al., 2005; Eggermont, 2012; Veterans Benefits Administration, 2014). Many types of peripheral injury have been understood to induce tinnitus, including damage to the cochlea by intense sound or ototoxic medications and destruction of the auditory nerve by cochlear ablation or nerve transection (Lee and Godfrey, 2014). The pathophysiological mechanisms by which tinnitus develops are only poorly understood. In order to further clarify the pathogenesis, a need has been expressed for a better understanding of the rebalancing of excitatory and inhibitory signaling mechanisms that occur after peripheral injury (Gold and Bajo, 2014). One of the current, prominent hypotheses of tinnitus development is that, after being triggered by peripheral injury, tinnitus may result from a maladaptation of the central auditory system to this peripheral dysfunction (Auerbach et al., 2014), and that one of the mechanisms by which this occurs is a decrease in inhibitory neurotransmission. The major structures that play a role in transmitting neural activity through the ascending central auditory system include the cochlear nucleus and superior olivary complex of the pons-medulla region, the inferior colliculus of the midbrain, the medial geniculate nucleus of the thalamus, and the auditory cortex.

One difficulty in studying tinnitus is its complexity. Tinnitus, as a symptom, can occur or change after various events such as exposure to very loud sound, changes in air pressure, certain medications, jaw movements, stress, or even spontaneously (Henry et al., 2005). The characterization of their tinnitus varies greatly among people, in loudness, pitch, and quality (Stouffer and Tyler, 1990; Eggermont, 2012). Tinnitus can develop suddenly or over a long period of time. The tinnitus that is most debilitating for people is that which persists chronically (Stouffer and Tyler, 1990; Shargorodsky et al., 2010). Although it is well established that most tinnitus results from damage to the peripheral auditory system, particularly the cochlea, it is not clear to what extent the pathophysiology progresses upward through the central auditory system or downward following changes in the cerebral cortex (Eggermont, 2012). Behavioral models of tinnitus have been developed in animal studies, but the characteristics of the tinnitus that the animal may be hearing and the extent to which it corresponds to the tinnitus that people find bothersome are difficult to assess experimentally (Eggermont, 2012).

**Neurotransmitters of the central auditory system:** Most chemical data available for neurotransmitter systems after cochlear damage concern the amino acids, glutamate, γ-aminobutyric acid (GABA), and glycine. Glutamate is well established as an excitatory neurotransmitter of auditory nerve fibers (Wenthold, 1985) and probably also of other ascending auditory pathways, and both glycine and GABA are well established as inhibitory neurotransmitters in the central auditory system. Although not as strongly associated with signaling mechanisms of the central auditory pathway, other amino acids such as aspartate and taurine might be of significance. Some evidence exists that aspartate, which has a close metabolic relationship with glutamate, might serve as an auditory nerve neurotransmitter (Wenthold, 1985), and that taurine, in addition to its relatively high concentration in glia, can have effects at GABA and glycine receptors

(Albrecht and Schousboe, 2005). Other neurotransmitters that have received less study may also be involved in auditory disorders; these include acetylcholine, serotonin, norepinephrine, dopamine, neuroactive peptides, and opioids (Romand and Avan, 1997; Eggermont, 2012).

Studies of neurochemical alterations associated with hearing disorders generally involve measurements of chemistry following damage to the peripheral part of the auditory system, particularly the cochlea of the inner ear. Measurements of central auditory function have particularly focused on synaptic chemistry, including neurotransmitter level, synthesis, receptors, release, and uptake (Eggermont, 2012; Lee and Godfrey, 2014). In order to fully understand the effect of peripheral damage on the central auditory system, measurements need to be made at a variety of times after the damage, since the various central effects may develop over a short or a fairly long time. For example, changes in electrical activity in the central auditory system may occur quickly after peripheral damage because of the distorted activity patterns sent to the brain, whereas neural degeneration and changes in synaptic function and chemistry may occur more gradually. Some types of tinnitus may develop very rapidly after peripheral damage, whereas others may develop more gradually, even over months or years (Stouffer and Tyler, 1990; Henry et al., 2005; Shargorodsky et al., 2010; Eggermont, 2012). Because the most debilitating types of tinnitus are chronic and persistent, it may be most appropriate to measure chemical changes at long times after peripheral damage in order to identify those which underlie the chronic symptoms.

**Cochlear damage effects on central auditory chemistry:** We recently reviewed available studies on neurochemical changes in the central auditory system after cochlear damage, so that the previous work in this field could be compared and categorized based on the type of cochlear injury, species of animal subject, neural structure, post-insult survival time, and aspect of chemistry measured (Lee and Godfrey, 2014). Previous reviews have reported chemical changes as simply increases or decreases (Eggermont, 2012; Gold and Bajo, 2014), but we presented the actual percent change from the values in control or sham-lesioned animals to provide a more objective picture of the existing evidence, so that readers can judge for themselves the significance of the findings.

In **Figure 1**, we present some of the noteworthy patterns of changes in amino acid levels in the cochlear nucleus following three types of cochlear damage. There are distinct effects on the neurochemistry based on the type of cochlear damage. For example, the effects of intense sound exposure on aspartate and glutamate levels were typically increases throughout the cochlear nucleus and, in fact, the entire central auditory system (Lee and Godfrey, 2014), whereas the changes measured after surgical cochlear ablation or carboplatin administration were typically decreases in the parts of the cochlear nucleus receiving major innervation from the auditory nerve (AVCN, PVCN, and DCNd). The patterns of change for GABA, glycine, and taurine after cochlear damage were less consistent, although taurine levels increased after carboplatin treatment in regions heavily innervated by the auditory nerve and decreased in all regions after intense sound exposure, including the more central auditory structures (Lee and Godfrey, 2014).

The idea that tinnitus may result from a decrease in inhibitory neurotransmission is not definitively supported by these results, in that types of cochlear damage that can lead to tinnitus did not consistently produce decreases in levels of amino acids involved in inhibitory neurotransmission. The situation is not simplified by looking at results for other characteristics, such as amino acid receptors, rather than levels. For example, although glycine receptors consistently decreased in the cochlear nucleus, lateral
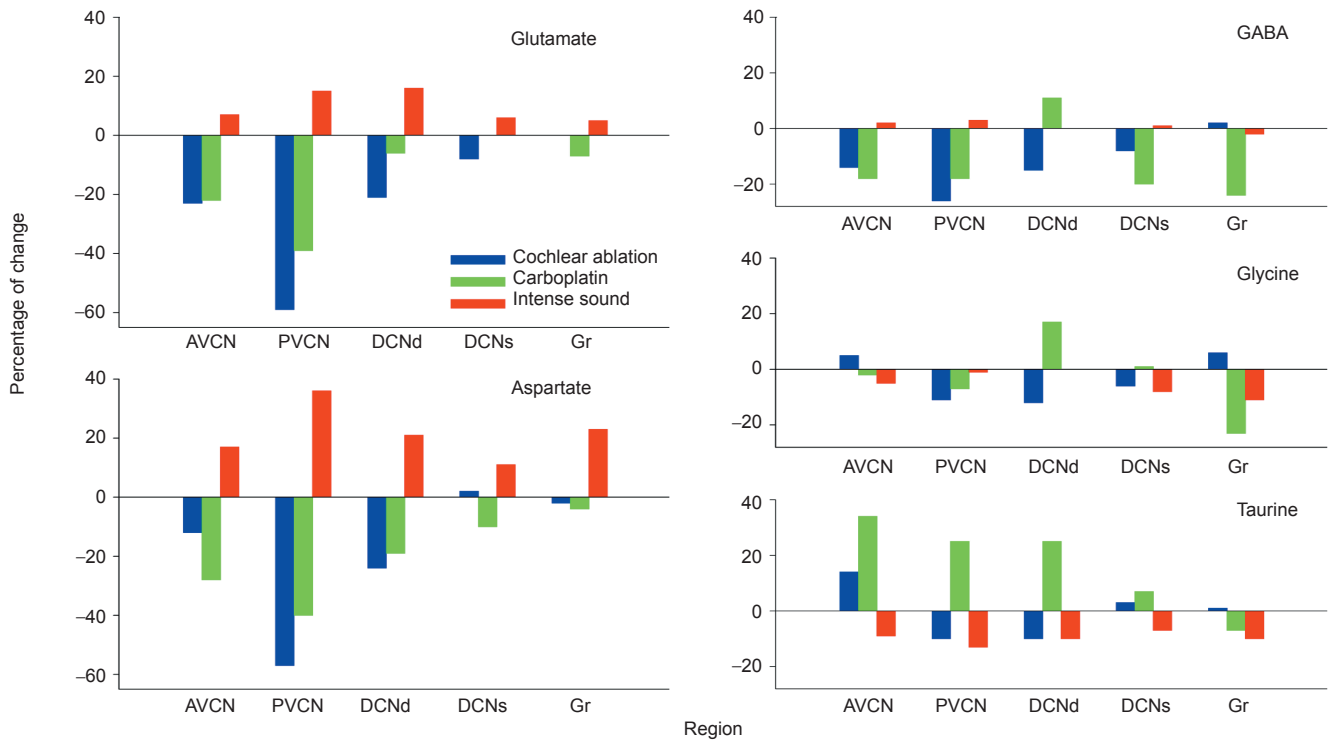
**Figure 1 Percent change from control of five amino acid levels in cochlear nucleus regions of animals at long times (> 2 months) after cochlear damage.**

Types of cochlear damage included: complete ablation of the cochlea, damage resulting from systemic administration of carboplatin, and damage resulting from exposure to intense sound. Regions studied included the anteroventral cochlear nucleus (AVCN), posteroventral cochlear nucleus (PVCN), deep (d) and superficial (s) parts of the dorsal cochlear nucleus (DCN), and granular regions (Gr). *Granular region data after carboplatin were obtained at 1.5–2 months (mid time point of Lee and Godfrey, 2014) after administration. **Absence of graph bar indicates that there was no change from control.
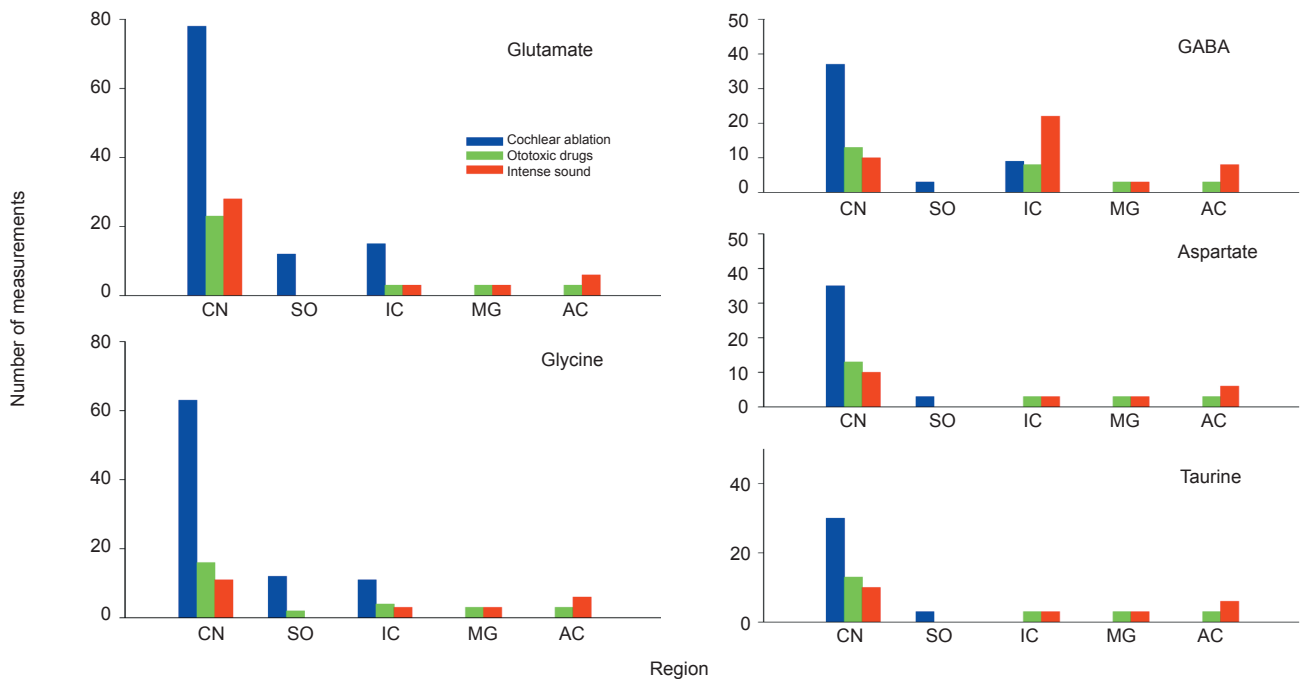


**Figure 2 Number of measurements of neurotransmitter characteristics for five amino acids at different levels of the central auditory system in the current scientific literature.**

Data for three different types of cochlear damage are shown. Measurements were tabulated from those presented in Lee and Godfrey (2014). Data for all subregions of each neural structure were combined to provide totals for the five major central auditory structures. CN: Cochlear nucleus; SO: superior olive; IC: inferior colliculus; MG: medial geniculate; AC: auditory cortex.

superior olivary nucleus, and inferior colliculus after cochlear ablation, and GABA receptors decreased in the inferior colliculus at short times after intense sound exposure, GABA receptors consistently increased in the inferior colliculus at longer (mid) times after intense sound exposure (Lee and Godfrey, 2014). Overall, the impression gained was that any imbalance of excitatory and/ or inhibitory neurotransmission could result in tinnitus.

The evidence compiled in our review shows the variety of chemical changes that can occur from cochlear injury, not only for amino acids, but also for acetylcholine, norepinephrine, and serotonin. One of the reasons that cochlear ablation is implemented experimentally is that it represents the extreme end of a potential gradient of cochlear injury, whereas other types of cochlear injury, such as from intense sound or ototoxic drugs, represent partial, or incomplete injuries, which are much more common causes of hearing disorders in society. Our review of current evidence demonstrates that the chemical effects of the different types of cochlear injury do not reflect a gradient of change based on the extent of injury, such that larger injuries produce larger effects of the same type as smaller injuries. Instead, injuries resulting from different causes may even produce opposite directions of chemical changes.

**Further research: Figure 2** visually represents the number of measurements reported in the current body of literature for five amino acids that appear to have important roles in the central auditory system (Lee and Godfrey, 2014). The number of measurements gathered so far is quantitatively greater for: glutamate and glycine than for other amino acids, the cochlear nucleus than for other regions of the central auditory system, and cochlear ablation than for other types of damage. There is clearly a need for more data for all types of cochlear damage in the superior olive, medial geniculate, and auditory cortex. For the cochlear nucleus, more data are needed for ototoxic drugs and intense sound. For the inferior colliculus, there is a need for more data for each type of cochlear damage, except possibly for GABA after intense sound.

Our review of the current body of scientific literature on neurotransmitter-related changes in the central auditory system after peripheral damage demonstrates value in further investigation of neurochemicals that may participate indirectly in neurotransmission or in neuromodulation in the central auditory system, such as aspartate and taurine. Results of such studies may reveal a clearer picture of the mechanisms underlying hearing disorders such as tinnitus. Based on the evidence of neurochemical changes after cochlear injury, the predominant idea that an overall reduction in inhibitory neurotransmission (disinhibition) could underlie the increased spontaneous activity occurring in the central auditory system may not account for the entire picture. Opposing changes in excitatory and inhibitory synaptic function in response to peripheral cochlear injury may be a more accurate representation of the pathogenesis of hearing disorders, but even such types of explanations may be too simplistic. One of the challenges in interpreting the significance of the results from our review of chemical changes after cochlear injury is the multiple spatial, temporal, and chemical factors related to how, when, and where the neurochemical of interest is measured, as well as possible species differences that complicate application of animal-study results to humans. The complex nature of the interactions affected by these factors requires further research. The studies investigating the neurochemical changes underlying tinnitus comprise one component of a large body of hearing disorder-related research. Corrective surgical or medical treatment for many hearing disorders, such as tinnitus, does not currently exist (Henry et al., 2005; Eggermont, 2012). As the scientific understanding of the pathogenesis of tinnitus and other hearing disorders progresses, the pathway towards improved prevention, detection, and treatment for these conditions could be made clearer.

To the best of our knowledge, our review of the current scientific literature concerning the effects of cochlear damage on chemistry in the central auditory system is the first of its kind. While conducting this review, we had difficulty in locating relevant studies of interest through standard electronic-based search engines, such as PubMed. One reason for this was the myriad of search terms and keywords used to categorize studies related to this field. Difficulty in identifying such studies could hinder the ability of future investigators to conduct a systematic review (Khan et al., 2003) of the relevant literature in order to comprehend the current state of the science, and to appropriately design studies that may advance the knowledge in this field. This problem is understandable given the relative newness of this field of study, and has also been noted from a clinical perspective (Henry et al., 2005). Now may be a good time for investigators to agree upon a more standardized terminology to categorize chemical effects in the central auditory system after cochlear damage.

**Augustine C. Lee**[*], **Donald A. Godfrey**

**Department of Neurology, University of Toledo College of Medicine, Toledo, OH, USA; Division of Otolaryngology and Dentistry, Department of Surgery, University of Toledo College of Medicine, Toledo, OH, USA**

**\*Correspondence to:** *Augustine C. Lee, M.D.,*
*Augustine.Lee@rockets.utoledo.edu.*

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