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Tinnitus: A Philosophical Problem

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Abstract: Anatomical, physiological and metabolic properties of tinnitus have been identified and a comprehensive theory is immerging. The key elements and their interaction are presented in a general fashion highlighting areas of concern such as needed details of individual biosusceptibility and the need for continued tinnitus modeling for predictions as an aid in the development of effective treatment modalities. Nonetheless, there remains something of the uniqueness of tinnitus as a personal experience. The use of the final common pathway (FCP) as a unifying principle in diagnosis and treatment is presented.

Key Words: final common pathway; model; theory; tinnitus

The philosopher Nagel [1] posed the question "What does it to feel like to be a bat?" His point was that we, as humans, are bound by our species perspective and the subjective character of our experiences, feelings, and consciousness. It is true that bats have evolved species-specific adaptations; nonetheless, these have arisen from a common mammalian plan. True, the bats have a stiffer tympanum, but we mammals all share a triossicular system. Bats echolocate [2], but humans can use ultrasound for mobility. Although we generally don't catch moths in our mouths, we can find our way alone, by an ultrasonic device, to a restaurant [3]. Bats also have an expanded frequency representation in their nervous system for processing their echo frequencies, a capacity that we, as humans, don't exactly share. However, some tinnitus patients do have, for example, an expanded area in their auditory cortex for their tinnitus frequency [4]. Perhaps we may know something of what it is to be a bat, but the Nagel question should be recast as "What does it feel like to be a severe tinnitus sufferer?"

Those who have experienced transient tinnitus might respond to that question by stating that surely they know; but do they, if they have never experienced severe disabling tinnitus? This is not just a fundamentally philosophical problem, although it could be, but a perceptually complex question based on our physiology. That is to say, how can one internally experience something that does not exist outside his or her head and only inside another's?

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AN OUTLINE

To explore this basic question, a general scheme of the genesis of subjective tinnitus is presented in Figure 1. Focusing on the left side reveals three discrete elements: in A, the exposure, the individual, and the pathology, all corresponding to B, the source, the initial and subsequent (Nth) biological responses, and tinnitus disease. Part C identifies the pathophenotype and the genotype (group and species) to be considered with implications for predictability, models, and biosusceptibility. The animal model (D in Figure 1), as it will be argued from an evolutionary perspective, must be a mammal. Thus, tinnitus is as much a marker of class Mammalia as are fur, sebaceous glands, and a triossicular middle ear—a point never considered in biological classification systems.

The overwhelming common source of subjective tinnitus is noise exposure; although the cause in some cases is not known (i.e., idiopathic), the mechanism of tinnitus is far more valuable for diagnosis and treatment [5–8]. Typically, noise exposure produces a physiological dynamic over different time scales. The initial biological response to the exposure is cochlear, but it also occurs in the central pathways [9–11]. With repeated exposures, other biological responses that occur cascade to induce changes at the hair cell, nerve, and nuclei levels, altering cortical function [12]. That is to say, the summed biological response to the exposure is spatial in the auditory nervous system. As the biological responses expand in the nervous system, the effect in an affected individual

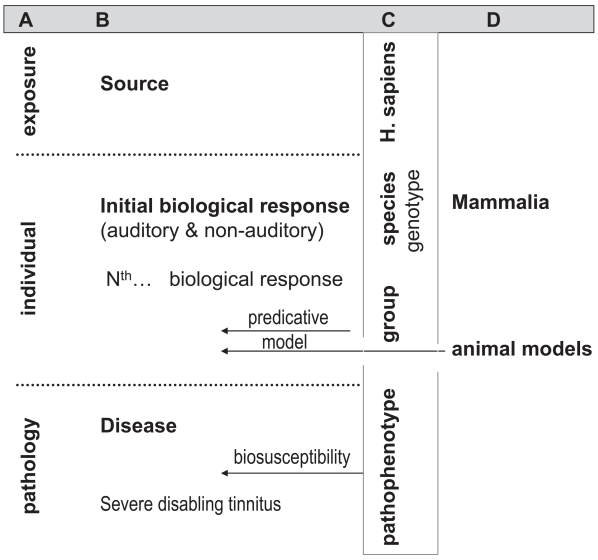

Figure 1. Conceptual model of tinnitus based on exposure and biological response in individuals, groups, and species.

can transition into a disease warranting treatment. In the simplest terms, the biological responses are additive, and their effect is cumulative, eventually exceeding the threshold of pathology. The progression of tinnitus in individuals has been well documented [13].

At another level, the phenomenological analysis of many affected individuals allows generalization and theory formulation of the natural history of tinnitus, providing some measure of predictability and modeling. Further, group analysis can also lead to an understanding of biological susceptibility, possibly determining who is at risk for the severest disabling form of tinnitus. The group data address the percentage of cases that might be expected (prevalence) and, possibly, their characteristics [14]. Knowing the natural history of tinnitus in its commonest and severest forms leads to strategies for tinnitus mitigation and restoration of psychological quiet. There is hope that proper selection of animal models may yield additional clues to the neural mechanisms of tinnitus [15].

BIOLOGICAL RESPONSE: ANIMAL MODELS

The "exposure" element in Figure 1A can be the result of a source, which in the case of intense noise is hearing loss. For reasons to be developed in more detail later, only mammals are acceptable choices for tinnitus models after noise-induced hearing loss. Modeling involves creating what is thought to be tinnitus in animals and developing strategies to limit biological responses (see Fig. 1B) in the animal brain. The animal approach that was first successfully applied to identify subjective tinnitus was the lick suppression technique [16,17]. Animals are water-deprived, then allowed to lick water to satiate their thirst. Animals are kept in a sound-filled environment and shocked when the sound is terminated, thus associating silence with pain (using classic conditioning to produce an eventual fear of silence). Daily doses of sodium salicylate induced hearing loss (primary action being on the outer hair cells) and tinnitus, based on changes in lick suppression and extinction. Rat tinnitus is between 11 and 16 kHz, not unlike that in humans [18,19].

These studies naturally lead to an animal model for central tinnitus, a model that attempts to specify mechanisms of auditory pathway changes that generally accompany hearing loss. Three events occur after hearing loss: (1) increased spontaneous firing rates in auditory neurons; (2) decreased excitation from the ear in the frequency range of hearing loss, resulting in less central inhibition in the central nervous system; and (3) reorganization of the normal cortical map in the auditory cortex such that the frequencies near the edge of the hearing loss are over-represented [20,21]. The increased spontaneous firing rate may be interpreted by the brain as actual sound, especially with synchronous spontaneous firing, and *that* could be the first manifestation of tinnitus [22]. Decrease in central inhibition is also thought to lead to inappropriate neuroplastic changes in tinnitus, with alteration in γ-aminobutyric acid (GABA) regulation as a potential mechanism [23]. The plasticity of the auditory cortex after hearing loss is well documented [21]: The neurons sensitive to the frequencies coded in the region of cochlear damage reprogram lower in frequency. That is to say, neurons shift their frequency response lower such that the frequency boundary of the cochlear loss becomes over-represented in the cortex. Thus, there are more cortical neurons responsive to the edge of the hearing loss in the cochlea.

A variation on this process was reported in human tinnitus patients with mild hearing loss. In some patients, reprogramming in the cortex actually increased the frequency representation of the tinnitus frequency by twofold [4]. Additionally, cortical neurons exhibit increased excitation likely resulting from the GABAergic effect previously noted. Further still, hearing loss–induced auditory nerve fibers' higher spontaneous and driving rates can lead to plastic changes such in other auditory sites as the inferior colliculus and the thalamus [24–26]. In fact, the decrease in inhibition, a function of the inhibitory neurotransmitter GABA, is especially marked in the inferior colliculus [26]. A biochemical marker, the $GABA_A$ receptor, has been identified [27]. These secondary central biological responses (see Fig. 1B) to tinnitus (overrepresentation of the tinnitus frequency and increased

excitation) could be the source of the tinnitus image that triggers the limbic system to respond, completing the final common pathway (FCP) in tinnitus patients [11,13].

Preventing hearing loss by controlling the "exposure" and averting any biological response (see Fig. 1B) is the most effective tinnitus control, but often that is simply not possible. A logical place to intervene in the tinnitus process after the exposure has taken place is altering the decrease in excitation owing to hearing loss such that the neural cascading of biological responses is averted. An intervention of this sort was first implemented by using cats as models for tinnitus. Noreña and Eggermont [25] reported that cats exposed to a traumatizing noise and immediately placed in a 40-dB high-frequency sound environment had much less hearing loss as compared with similarly exposed cats placed in a quiet environment. The hearing loss in the quietly reared cats ranged from 6 to 32 kHz, with a loss, on average, of 40 dB. In contrast, the hearing loss in cats in the high-frequency sound environment was restricted to 6–8 kHz at a level near 35 dB. Despite the restricted hearing loss for the cats subjected to high-frequency stimulation in the 6- to 8-kHz range, no auditory cortical reprogramming was found, suggesting that the high-frequency stimulation prevented the expected reorganization.

With sufficient exposure, the central auditory characteristics of noise-induced hearing loss have always been thought to encompass reorganization of the tonotopic map in the auditory cortex and increased brainstem neuron synchronous spontaneous firing rates. With hearing loss, the neurons shift their best response lower in frequency, approximating the new sensitivity of the ear. Keeping cats, after noise trauma, in a high-frequency-enriched environment prevented tonotopic map reorganization and reduced the expected hearing loss due to the noise as contrasted with cats with the same exposure but kept in quiet. That is to say, high-frequency stimulation maintained normal cortical organization and essentially improved hearing (by reducing expected hearing loss). Noise-exposed cats kept in the high-frequency environment displayed normal spontaneous firing rates. The authors interpreted the perseverance of normal spontaneous firing rates as an indication of the absence of tinnitus. These are very important observations, because what is implied, at least in the cat model, is that the neural biological responses (see Fig. 1B) to hearing loss can be averted with only postexposure high-frequency sound, suggesting the conclusion that tinnitus is not necessarily an end result of an "exposure" (i.e., not a phantom stimulus). Keeping cats in quiet or providing low-frequency stimulation was not effective in preventing hearing loss and neural map changes.

The loci of action of high-frequency therapy can be at the peripheral or central level (or both). Stimulation can improve microcirculation, possibly restoring damaged hair cells [28]. The strong central effect is likely from increased stimulation in retrograde areas, which reverses the decreased spontaneous and driving firing rate of auditory neurons (exposure), and that increase in excitation has a cascading effect on the neuraxis to maintain the cortical frequency map. Studies [25,26] of high-frequency stimulation for tinnitus mitigation are very encouraging in that the protocol appears to be effective in the cat model, with seemingly no negative side effects from listening to moderate-level high-frequency sound. What is clinically important is that the map can be targeted using external sound, and this is a viable treatment modality for humans with severe disabling tinnitus (see Fig. 1 B,C) [28–31].

PREDICTIVE ANIMAL TINNITUS MODELS: MAMMALS

There are two lines of descent from stem reptiles: the archosaurs (crocodiles and birds) and the mammals (sauosaus). The ear evolved in parallel in each line, with a very important distinction: The archosaur line can regenerate hair cells, and mammals cannot. If an animal recovers its hearing by hair-cell regeneration, tinnitus—if it exists—would be acute. In contrast, the mammalian line, dating back to dinosaurs, has sacrificed the ability to regenerate hair cells. Regeneration involves supporting cells in nonmammals but, in mammals, these cell are highly specialized to enhance sound detection and discrimination that are the building blocks of accurate sound localization. Excluding the brief period of intense manmade noise, the likelihood of noise-induced hearing loss would have been small over 200 million years. What would have been the causative events: thunder, vocalizations? Only with the industrial revolution does the tradeoff of regeneration versus fine discrimination seem to come into question. Perhaps systems biology will lead to pharmaceuticals to turn back on the regenerating process [32].

INITIAL CENTRAL BIOLOGICAL RESPONSE

What are the biological responses active after noise exposure? Immunoreactivity recorded in the auditory and non-auditory brain sites [33] suggests specific sites with a very fast activation after just a single high noise exposure (10 kHz, 125–127 dB SPL, 4 h) which induces hearing loss and tinnitus, in a animal model, verified by auditory brainstem response (ABR) and lick suppression behavioral audiometry. The c-fos immunocytochemistry (FIC) technique identified active sites in the inferior colliculi, the auditory cortices, medial temporal lobe (MTL) system and the parabrachial nucleus (PN) [33]. Electrical

stimulation of the cochlea also evokes FIC in PN [34]; thus this nucleus, located near the inferior colliculus, can be considered sensitive to tinnitus [35] and a link to the auditory/frontal cortices, the MTL system (including the insula), and the cerebellum. The non-auditory sites, in the traditional sense, also contribute to conscious emotional behaviors, including stress and anxiety, that often are associated with severe tinnitus [12,21,36]. The amygdala and the PN, with its visceral connections, can induce the familiar autonomic nervous system and endocrine reactions also noted in severe tinnitus. The insula cortex is also well interconnected in the MTL system and may be a key component in maintaining emotional and addictive behaviors [35] heretofore generally overlooked in tinnitus circuitry. Hence, the initial biological response is a cascading of neural sites and physiology that changes over time—that is, neural plasticity.

CONCLUSION

The MTL system, as a central part of the FCP [13], is also auditory, as postulated more than 20 years ago [37], due to its interconnectiviness with both the lemniscal and extralemniscal pathways. The MTL plays a major role in creating the perception of severe disabling tinnitus. All these neural sites and their physiological responses at the electronically and molecular levels produce the tinnitus percept that still can only be imagined by someone without direct experience of severe disabling tinnitus. The rapid activation of the FCP with just one exposure raises the question of biosusceptibility. So, much like the bat, we know pathways, physiology, and acoustics, but what is it to really be like a bat or to have never-ending tinnitus? True understanding may just require direct experience.

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