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Animal models of tinnitus

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A B S T R A C T

Presented is a thematic review of animal tinnitus models from a functional perspective. Chronic tinnitus is a persistent subjective sound sensation, emergent typically after hearing loss. Although the sensation is experientially simple, it appears to have central a nervous system substrate of unexpected complexity that includes areas outside of those classically defined as auditory. Over the past 27 years animal models have significantly contributed to understanding tinnitus' complex neurophysiology. In that time, a diversity of models have been developed, each with its own strengths and limitations. None has clearly become a standard. Animal models trace their origin to the 1988 experiments of Jastreboff and colleagues. All subsequent models derive some of their features from those experiments. Common features include behavior-dependent psychophysical determination, acoustic conditions that contrast objective sound and silence, and inclusion of at least one normal-hearing control group. In the present review, animal models have been categorized as either interrogative or reflexive. Interrogative models use emitted behavior under voluntary control to indicate hearing. An example would be pressing a lever to obtain food in the presence of a particular sound. In this type of model animals are interrogated about their auditory sensations, analogous to asking a patient, “What do you hear?” These models require at least some training and motivation management, and reflect the perception of tinnitus. Reflexive models, in contrast, employ acoustic modulation of an auditory reflex, such as the acoustic startle response. An unexpected loud sound will elicit a reflexive motor response from many species, including humans. Although involuntary, acoustic startle can be modified by a lower-level preceding event, including a silent sound gap. Sound-gap modulation of acoustic startle appears to discriminate tinnitus in animals as well as humans, and requires no training or motivational manipulation, but its sensitivity, reliability, mechanism, and optimal implementation are incompletely understood. While to date animal models have significantly expanded the neuroscience of tinnitus, they have been limited to examining sensory features. In the human condition, emotional and cognitive factors are also important. It is not clear that the emotional features of tinnitus can be further understood using animal models, but models may be applied to examine cognitive factors. A recently developed model is described that reveals an interaction between tinnitus and auditory attention. This research suggests that effective tinnitus therapy could rely on modifying attention to the sensation rather than modifying the sensation itself.

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Abbreviations: A1, primary auditory cortex; BBN, broadband noise; dB SPL, decibel sound pressure level re 20 μPa; DCN, dorsal cochlear nucleus; GABA, gamma-amino butyric acid; GPIAS, sound gap inhibition of the acoustic startle reflex; MGB, medial geniculate body of the thalamus; MGBv, ventral (lemniscal) nucleus of the medial geniculate body; PPI, pre-pulse (sound) inhibition of the acoustic startle reflex; SIPAC, schedule (food) induced polydipsia avoidance conditioning

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1. Chronic subjective tinnitus

Chronic subjective tinnitus is a perception of sound when there is no internal or external acoustic source. It is a common condition, affecting perhaps one third of the adult population, with 3–5 percent of those affected seeking professional treatment (Hoffman and Reed, 2004; Shargorodsky et al., 2010; Sindhusake et al., 2003). Although the common name of "ringing in the ears" implies that the hearing organ is the source of tinnitus, this is not entirely accurate. It is true that tinnitus, more often than not, accompanies hearing loss, and is therefore associated with ear pathology (Roberts et al., 2010). It is also true that a damaged ear may contribute to tinnitus pathophysiology (Mulders and Robertson, 2009). But the actual source of the sensation, i.e., the generator of the tinnitus, is in the central auditory system (Berliner et al., 1992; House and Brackmann, 1981). Contemporary evidence, obtained from human imaging studies as well as from animal research, suggests that the physiological condition responsible for tinnitus is more complicated than intuition would suggest, and that it is distributed across a neural network encompassing both traditionally defined auditory brain areas as well as non-auditory areas (Brozoski and Bauer, 2014, Brozoski et al., 2007a; Rauschecker et al., 2010; Roberts et al., 2010). Two issues of primary concern are that tinnitus is typically resistant to treatment and its physiological substrate is incompletely understood. These issues no doubt are linked and provide the impetus for using animals to further understand the neuroscience of tinnitus perception. Typically, advances in understanding disorders are made when laboratory animal models become available. For over a century, nearly every Nobel Prize in Medicine has been awarded for research that, at least in part, used animal models (Research, 1979). This article will thematically review animal models of tinnitus, focusing on general and specific features, and will examine the advantages and limitations of several models. To begin, two fundamental questions should be answered. Can animals experience tinnitus, and how can this be objectively known?

2. Can animals experience tinnitus?

Tinnitus is a primitive percept it is almost invariably associated with hearing loss (Roberts et al., 2010). Since tinnitus directly, or indirectly, emerges as a pathological consequence of sound transduction degradation, there is no *a priori* reason why animals, who share many features of their auditory system with humans, should not experience tinnitus. Neuropathic pain is in many ways similar to chronic tinnitus and in fact a hypothesis has been advanced that tinnitus might be the perception of chronic pain in the auditory system (Moller, 2000). Both tinnitus and neuropathic pain are subjective sensations that cannot be directly measured and neither typically has an immediate physical correlate. While pain and tinnitus often result from damage to the periphery, they frequently persist well after the immediate damage is resolved. If tissue damage can cause pain, it is likely that damage to a specialized sensory organ such as the cochlea can similarly produce acute as well as lingering pathological effects. This certainly is true in humans, and it appears that neither cognitive or language function is required for the sensation of tinnitus. Given that humans and animals have many physiological systems in common, it is entirely plausible that they share many sensory states. The auditory systems of mammals such as mice, rats, guinea pigs, chinchillas and cats, have been studied extensively. Many aspects of auditory physiology were first determined in animal experiments, and only later confirmed in humans. For example, the fundamental process of sound transduction, the neural extraction of acoustic information in the brainstem, and central auditory organization, all were understood using animal studies. Therefore, if tinnitus arises because of basic pathological mechanisms at one or more levels in the auditory pathway, tinnitus should appear in animals that have auditory system commonality with humans.

3. An overview of animal models

Animal models have been developed to provide reliable objective measurement of tinnitus in nonverbal subjects. The advantage of animal studies over human clinical studies are several, the most notable being: (a) direct control over history and etiology, (b) availability of a large number of experimental tools, extending from behavioral to molecular, (c) when required, use of invasive methods not appropriate for humans, and (d) the random assignment of subjects to experimental and control groups thus enabling the use of more powerful inferential statistics as well as attribution of cause. The central problem all models face is establishment of reliability and validity (Brozoski and Bauer, 2014). A somewhat easier problem to solve is tinnitus induction, since many causes of tinnitus have been described for humans, and most of them are relatively straightforward to apply to animals.

The first published animal model of tinnitus was that reported by Jastreboff and colleagues (Jastreboff et al., 1988). A key feature of this model, and one that has been incorporated into all subsequent models, is that while tinnitus might sound like anything to an animal (or human), by definition it cannot sound like silence. Jastreboff et al. exploited this feature by testing rats that were licking a spout to obtain water, with randomly inserted periods of silence interrupting otherwise continuous background sound (broad-band noise, BBN, at 60 dB, SPL). Prior to the test, all rats had been given a mild electric shock when drinking during the sound-off periods. Some of the animals were then given a high (300 mg/kg) systemic dose of sodium salicylate, a congener of aspirin, before testing. Aspirin at high doses invariably produces temporary subjective tinnitus in humans. The rats on salicylate behaved as though they could not hear the silent periods, and continued licking (during testing the electric shock was turned off). In contrast, the non-salicylate control animals abruptly stopped licking during the silent periods. The interpretation was that the salicylate-treated rats could not hear the silent periods because of their tinnitus. Lick suppression in control animals persisted for days, but eventually