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ANIMAL BEHAVIORAL MODELS OF TINNITUS

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Abstract

The pathophysiology of tinnitus is poorly understood and treatments are often unsuccessful. A number of animal models have been developed in order to gain a better understanding of tinnitus. A great deal has been learned from these models regarding the electrophysiological and neuroanatomical correlates of tinnitus following exposure to noise or ototoxic drugs. Reliable behavioral data is important for determining whether such electrophysiological or neuroanatomical changes are indeed related to tinnitus. Of the many documented tinnitus animal behavioral paradigms, the acoustic startle reflex had been proposed as a simple method to identify the presence or absence of tinnitus. Several behavioral models based on conditioned response suppression paradigms have also been developed. In addition to determining the presence or absence of tinnitus, some of the behavioral paradigms have provided signs of the onset, frequency, and intensity of tinnitus in animals. Although none of these behavioral models have been proved to be a perfect model, these studies provide useful information on understanding the neural mechanisms underlying tinnitus.

Key word: Tinnitus; Behavioral model; Acoustic startle; Noise exposure; Salicylate

Tinnitus is a symptom of many pathological conditions and is an auditory phantom sensation experienced when no external sound is present. Tinnitus occurs with a surprisingly high prevalence affecting about 35% of the general population, with 10%-15% of individuals experiencing prolonged tinnitus requiring medical evaluation [1-3]. For 10% of the population tinnitus has a significant impact on their quality of life [4].

Over the years, progress has been made using electrophysiology, cell biology, molecular biology, and other techniques to understand the neural correlates of tinnitus. A number of methods have been used to reduce the symptoms of tinnitus, including auditory masking procedures [5-9], electrical stimulation[10-14], and pharmacological treatments [1, 15-20]. The phantom perception of tinnitus often begins with the onset of hearing loss induced by acoustic overstimulation[21-25] or ototoxic drugs[23, 24, 26, 27]. However, the exact causes of tinnitus remain largely unclear.

A number of interesting neurophysiological changes have been identified regarding tinnitus in animal models. For example, an increase in neuronal spike synchrony has been observed in auditory cortex and is thought to be related to tinnitus [28]. Additionally, an increase in spontaneous firing rates in the auditory cortex and inferior colliculus has also been associated with tinnitus[29, 30] [28, 31-36]. However, whether or not these changes are truly related to tinnitus cannot be confirmed unless a behavioral testing is used to evaluate the presence or absence of tinnitus. Therefore, it is important to employ behavioral techniques that permit tinnitus to be assessed in individual animals treated with a particular tinnitus inducing agent in order to determine if tinnitus is present or absent at a particular time[36-41]. Because tinnitus is subjective in nature and there is no objective test of tinnitus, it can therefore be difficult to quantify in an animal model. Currently, there are several useful animal behavioral models that

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use “animal behavioral changes” which may associate with tinnitus to study the underlying neural mechanisms and potential treatments of tinnitus.

Tinnitus model based on acoustic startle reflex paradigm

In recent years, the acoustic startle reflex (ASR) became a popular technique for tinnitus assessment[36, 42]. This behavioral model confers a significant advantage than the time-consuming behavioral approaches utilizing basic mechanisms of conditioning[37, 38, 40, 42-46]. During the test, animals were placed in a holder on top of a piezo-electric transducer that measures the animal's motoric reflex to a sudden loud sound (Figure 1A). The technique relies on a reduction of the ASR by a preceding silent gap in an otherwise constant acoustic background (Figure 1B). An animal is presumed to have tinnitus if a preceding gap fails to reduce the startle reflex due to tinnitus “filling in” the silent gap (Figure 1C-D). This method has been described and used in a number of studies [45] [42, 47].

Prepulse inhibition of the ASR has been used to assess tinnitus in different laboratory animals. This technique doesn't require complex behavioral manipulations (food or water deprivation, finely tuned shock parameters, variable reinforcement schedules, etc.) and also doesn't require long durations to train the animals. Additionally, ASR does not rely on learning, memory or motivation. The startle neural circuit, its modulation using background sounds, and stimulus parameters has been studied extensively[42, 48-53]. It's easy for newcomers learning to correctly apply gap detection techniques for tinnitus assessment in different animals. This method has been used to assess tinnitus induced by ototoxic drugs or acoustic trauma in mice [54, 55] and rats [36, 42, 56-58].

Although prepulse inhibition of the ASR seems to be an efficient and reliable method, a number of questions have arisen regarding the use of the paradigm in behavioral models of tinnitus. One question is whether changes in prepulse inhibition are due to tinnitus or simply due the hearing loss. A number of studies have demonstrated a reduction in startle amplitude following use of noise exposure to induce tinnitus suggesting that hearing loss

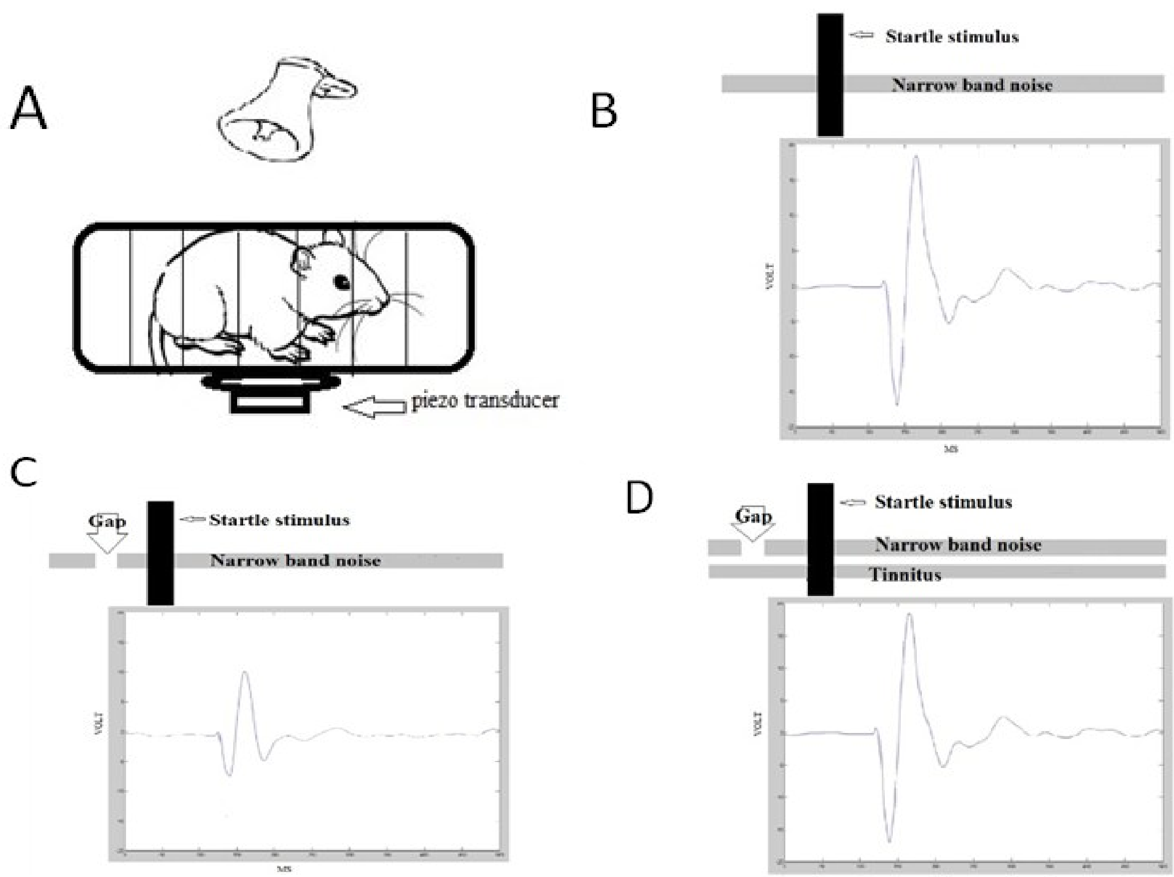

Figure 1. (A) Animals are placed in a holder on top of a piezo-electric transducer. (B) Acoustic startle reflex with constant acoustic background. (C) Reduction of the acoustic startle reflex by a preceding silent gap in an otherwise constant acoustic background. (D) Tinnitus 'filling in' the gap, no reduction of the acoustic startle reflex by a preceding silent gap in constant acoustic background.