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REVIEW / DERLEME

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# Tinnitus Models in Experimental Animals

## Deney Hayvanlarında Tinnitus Modelleri

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## Abstract

Tinnitus can be defined as an imaginary sound perception in silence without any acoustic sound source in the external environment. Despite many years of human and experimental animal studies, its mechanism, pathophysiology and etiology are still debated. The perception of tinnitus differs between individuals in terms of intensity, frequency, temporal characteristics, and localization in the head or ear. Although it is easier to detect the presence and characterize tinnitus in humans in clinical practice and research, the use of experimental animal models is inevitable to determine the physiology of tinnitus, which significantly reduces the quality of life, and to study possible treatment methods. Although tinnitus can be induced in experimental animals by using salicylate or exposing them to noise, different techniques and methods have been used to determine the presence of tinnitus and its physiological characteristics. In this review article, it is aimed to present the tinnitus inducing methods in experimental animals used in the literature together with behavioral and electrophysiological methods used to determine the presence of tinnitus.

**Keywords:** Experimental animal, behavioral model, tinnitus

## Öz

Tinnitus dış ortamda herhangi bir akustik ses kaynağı olmaksızın sessizlikte algılanan hayali ses algısı olarak tanımlanabilmektedir. Uzun yıllardır yapılan insan ve deney hayvanı çalışmalarına rağmen oluşum mekanizması, patofizyolojisi ve etiyolojisi hala tartışılmaktadır. Tinnitus algısı sesin şiddeti, frekansı, zamansal özellikleri, kafa ya da kulakta lokalize olması ile bireyler arasında farklılık göstermektedir. Klinikte ve araştırmalarda insanlardaki tinnitus varlığını saptamak ve karakteristik özelliklerini belirlemek daha kolay olsa da, insan yaşam kalitesini önemli ölçüde azaltan tinnitus fizyolojisinin belirlenmesi ve olası tedavi yöntemleri üzerinde çalışılabilmesi için deney hayvanı modellerinin kullanımı kaçınılmazdır. Deney hayvanların salisilat kullanılarak ya da gürültüye maruz bırakılarak tinnitus oluşturulabilse de, oluşan tinnitus varlığının ve tinnitusun fizyolojik özelliklerinin belirlenmesi için günümüze kadar farklı teknik ve yöntemler ile çalışılmıştır. Bu derleme makalesinde literatürde kullanılan deney hayvanlarında tinnitus indükleyici yöntemler ile tinnitus varlığının belirlenmesinde kullanılan davranışsal ve elektrofizyolojik yöntemlerinin bir arada sunulması amaçlanmıştır.

**Anahtar Kelimeler:** Deney hayvanı, davranışsal model, tinnitus

## Introduction

Tinnitus can be defined as an imaginary perception of sound originating from the peripheral or central auditory system. It usually feels in silence without an acoustic sound source from the external environment and its symptoms effect an average of 10-15% of the population. The perceived sound is caused by an abnormality in the auditory system rather than a disease. The perception of tinnitus is distinguished by its intensity, frequency, temporal characteristics, localization to the head or ear and which differ between individuals and its mechanism is still unsolved exactly[1].

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Although there are many different classifications of tinnitus, the most common classification is objective and subjective tinnitus. Objective tinnitus is the perception of mechanically generated acoustic vibrational activity. It can also be heard by another person. It may be of vascular, muscular, skeletal or respiratory origin. It is usually caused by a mechanical cause related to the regular contraction of the middle ear muscles or is defined as pulsatile tinnitus synchronized with the pulse with the sensation of blood flow in the body[1]. Subjective tinnitus the most common type of tinnitus and heard only by individuals. Although there is no common opinion about its origin, it is thought that the corrective responses given by the central auditory system and limbic system to neural, cellular or functional impairments in the peripheral auditory system cause subjective tinnitus perception[1,2].

The main risk factors for tinnitus are hearing loss, aging, occupational or recreational noise exposure and drug use. Possible risk factors such as auditory system diseases, obesity, diet, smoking and alcohol consumption, head trauma, hypertension, hyper/hypothyroidism, genetic factors and viral infections have also been reported in the literature[3-5]. Tinnitus can be treated by eliminating or reducing the effects of potential risk factors. However, in some cases, tinnitus does not completely disappear and this condition, which negatively affects quality of life, is alleviated with long-term treatment strategies.

Although there are different opinions about tinnitus from prevalence to etiology, diagnosis and treatment/coping strategies, the subject of tinnitus remains up-to-date in the literature with both human and animal studies. Especially in recent years, experimental animal studies have helped to reveal details about tinnitus[6-8]. In this article, which was prepared to review tinnitus modeling methods in experimental animals, the substances used in tinnitus induction and behavioral and electrophysiological methods used in the evaluation of the presence of tinnitus are mentioned in the current literature.

### Experimental Animal Models of Tinnitus

Studies designed to determine the presence of tinnitus, to determine its characteristic features and to examine the changes occurring in the auditory system by behavioral and electrophysiological methods in humans are more easily organized than animal models. However, it is inevitable to use animal models to conduct experimental studies on tinnitus physiology and possible treatment methods. However, in this method, it is not as easy to determine the perceptual and neural characteristics of tinnitus in animals as in humans.

Rats (Long-Evans, the Sprague Dawley, Norway rat, the Wistar, the Fisher 344), mice, guinea pigs and cats were the experimental animals of choice in the literature for the induction and subsequent evaluation of tinnitus[9]. In a review prepared by Domarecka et al.[8], 36 studies evaluating the electrophysiologic testing method in experimental animals modeled for tinnitus were reviewed and it was reported that approximately 50% of the studies conducted in the last decade used male Spraque-Dawley rats. Despite all the studies, tinnitus induced by animal models is not exactly the same as tinnitus occurring in humans and therefore the use of animal models to understand the causes and treatments of tinnitus in humans is limited. Nevertheless, animal models are an important tool to investigate the mechanisms and treatments of tinnitus. There are different methods used to induce tinnitus in animals. In these methods, ototoxic (ear-damaging) compounds are used as tinnitus inducers such as salicylates, some antibiotics (e.g., gentamicin), chemotherapy drugs (e.g., cisplatin), painkillers (e.g., ibuprofen) and noise exposure, which can damage cells in the ear and cause hearing loss[10].

## Methods Used to Induce Tinnitus

### Salicylate

Salicylate is an active ingredient of aspirin. It's modest amounts has analgesic, antipyretic and anti-inflammatory effects[11]. However, excessive amounts can cause temporary moderate hearing loss, and a high-pitched perception of tinnitus in humans and animals[12]. Although the exact mechanism is not fully understood, it is thought that salicylates may cause hearing loss and tinnitus by accumulating in the fluid inside the ear or by disrupting the mitochondria in the cells of the auditory system[11]. Although it varies individually, it has been reported that salicylate-induced tinnitus in animals, as in humans, is usually in the high frequency range of 10-16 kHz or 7-9 kHz[10,13]. Furthermore, tinnitus associated with salicylates usually resolves spontaneously within a few days of stopping the medication[12].

In the study by Jastreboff et al.[14] was showed that intraperitoneal administration of sodium salicylate at a dose of 350 mg/kg cause to hearing loss and tinnitus development in rats. In addition, another study reported that the concentration of sodium salicylate in the blood reaches the highest value 2-4 hours after intraperitoneal injection and the drug completes its half-life 8-15 hours after injection[15]. In recent studies conducted for the same purpose, intraperitoneal sodium salicylate was used at different doses such as 400 mg/kg per day for 7 consecutive days[16], single dose 350 mg/kg[17], 5 days a week for 3 weeks and 200 mg/kg per day[18].

## Noise

Noise exposure is one of the main factors affecting hearing health in living organisms. The duration, intensity and type of exposure may vary with the damage to the auditory system. Noise exposure in the form of sudden acoustic trauma causes sudden and relatively permanent hearing loss and tinnitus, while prolonged and gradual exposure causes progressive hearing loss and tinnitus. This difference in the relationship between exposure and outcome has led to differences in noise-induced tinnitus models in the literature.

Domarecka et al.[8] reported that noise was used as a tinnitus inducer in 19 of 39 animal tinnitus modeling studies published in the literature in the last 10 years. The characteristics of the noise stimulus used vary as unilateral or bilateral, prolonged or sudden stimulation with different frequencies in the range of 8-16 kHz and different sound intensities in the range of 80-194 dB SPL[19-21]. The type of noise stimulus to be used should be determined according to the characteristics of the damage to be caused.

## Models Used to Determine the Presence of Tinnitus

## Behavioral Models

As mentioned above, although the use of experimental animal models is inevitable in determining the mechanism of tinnitus formation and treatment alternatives and protocols, whether determining the tinnitus in these models and some measurements are more difficult than the methods used in humans. Behavioral models are the primary method used to assess whether tinnitus occurs in experimental animals after exposure to tinnitus-inducing substances. The basis of behavioral models is the first models created by Jastreboff et al.[22] and Bauer et al.[23] and many new methods have been developed and introduced to the literature until today.

## Jastreboff's Conditioned Suppression Model

It is the first behavioral test used to evaluate tinnitus in experimental animals. Basically, it teaches the relationship between sound and drinking behavior after prolonged thirst and conditions the animal to drink water when it hears a sound. In this way, the animal is taught the difference between sound and silence. The method consists of 3 stages; 2-3 days of initial training, 4-5 days of Pavlov's conditioned suppression training, behavioral test 2 hours after salicylate administration. Before the initial training, the experimental animal keep under normal housing conditions for 18 hours without water, with 10 kHz 60 dB pure tone played in the background. The first phase of training lasted for 28 minutes with sound and 4 silent intervals of 30 seconds each for a total of 30 minutes. The training, which is applied for half an hour a day, continues for 3 consecutive days. In the second stage, which is Pavlov's conditioned suppression training, in addition to the first stage, conditioning is performed by giving a foot shock to prevent the animal's drinking behavior in the silent condition and water drinking behavior is taught only during the time it hears sound. The second phase continues for 4-5 days with periods of 30 minutes per day. In the last phase, the behavioral test phase, foot shock is not used and the behavior of the animal is recorded in sound and silent conditions (Figure 1). The number of water drinks in the sound and silent condition during the training process is proportioned and compared with the results of the third phase, the behavioral test phase, after the training. For learning, the suppression rate of drinking should be <0.5. If the water drinking behavior is greater than 0.5 in the test phase, it means that tinnitus has occurred[14,22,24].

## Bauer and Brazoski's Conditioned Avoidance Model

The method is based on Jastreboff's conditioned suppression method, which is based on the principle of teaching the difference between sound and silence. In this method, the experimental animal is taught to press the pedal for food in 60 dB SPL broadband background noise after prolonged fasting. In order to prevent the pedal pressing behavior in silence, a foot shock is applied randomly in 60 seconds of silence embed in the background noise during training process. The experimental animal is considered to be conditioned when there is a 25% decrease in pedal pressing

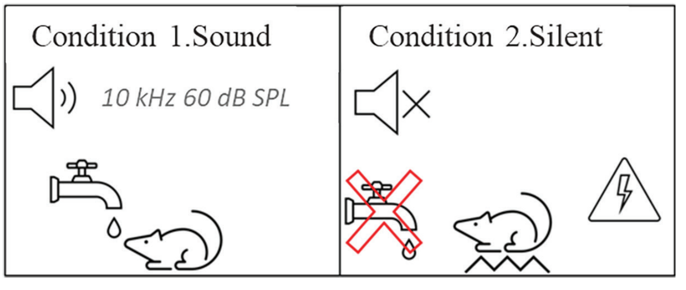


**Figure 1.** Jastreboff's conditioned suppression model

behavior during the training process. In the test phase, the foot shock is not applied and the evaluation is made on the basis of the fact that the experimental animal continues to press the pedal in silence if tinnitus occurs[23].

## Guitton's Conditioned Avoidance Model

Guitton et al.[25] developed a method that teaches experimental animals to avoid a 3.7 mA foot shock delivered from the cage floor in the presence of 10 kHz 50 dB SPL pure sound for 3 min by first performing a conditioning experiment. In previously developed methods, the foot shock given in silence is used in the audible condition in this method. Experimental animals are conditioned to climb a ladder positioned at the corner of the cage in the audible condition. Afterwards, as a result of 10 trials lasting 10 minutes, the experimental animal is considered to have learned the training when it avoids 80% of the foot shocks given with sound. When tinnitus is induced, the experimental animal is expected to spend more time on the ladder and avoid the cage floor due to the constant sound (Figure 2).

## Turner's Method for Suppressing the Startle Reflex

The startle reflex suppression method of Turner et al.[26] was designed on the basis of keeping cognitive and motivational variables under control, unlike other behavioral models that require training of the experimental animal. In this method, the experimental animal is not pre-trained for tinnitus assessment. It is basically depend on evaluation of the startle reflex to sudden sound. In the evaluation process, the experimental animal in a cage with a piezoelectric transducer at the base is randomly given 50 ms silent intervals in a continuously played 60 dB SPL narrowband sound and the pressure value of the startle pressure value is measured by giving 20 ms 115 dB SPL broadband sound during the silent interval. This startle pressure value is expected to decrease in animals with tinnitus.

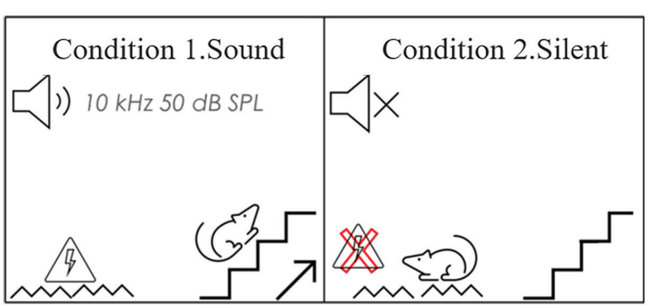


**Figure 2.** Guitton's conditioned avoidance model

## Guitton's T Water Maze Model

The water maze method is based on the principle that the experimental animal chooses between two options. Unlike other methods, it has some advantageous such as no deprivation or foot shock is applied. The method developed by Guitton and Dudai[27] uses a T-shaped pool into which a portable escape platform can be placed. The experimental animal is released from the starting arm into 21 degrees celsius water, and by positioning the exit platform in the pool to the right while it was sound and to the left while it was silence, they are taught the arm they should turn to in a sound and silent environment. The training continues for 3 days with a total of 12 condition sessions in the order of 3 audible and 3 silent conditions, 1 session per day. Researchers recommend the use of 6 or 10 kHz 45 dB SPL pure tone for the audible condition (Figure 3). During training, the average time to reach the platform in 12 trials and the percentage of correct decisions are used as learning criteria. Afterwards, the animals, which are thought to be induced by chemical or noise induced tinnitus, are left in the starting arm of the pool where there is no platform in any arm without background sound, and they are evaluated according to which arm they spend time in and where they look for the platform. The expected performance of the tinnitus-induced animal is that it behaves as if the background sound is given during training and spends more time in the right arm due to the tinnitus it hears.

## Rüttiger's Conditioned Avoidance Model

In this method, Rüttiger et al.[28] use a commercial conditioning cabinet designed for the purpose of their study. The base of the booth consists of bars suitable for foot shock application and a platform with a mechanical sensor on one side that serves as a resting place. The booth is divided into two short corridors by a wall in the center and contain a liquid feeder. And it has a photo sensor at

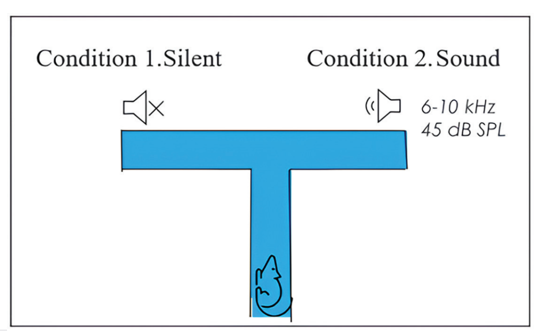


**Figure 3.** Guitton's T water maze model

the end of the corridors for monitoring animal movements. Reward is water containing 3% sucrose in the liquid feeder. In this method, training lasts 30-60 minutes a day, five days a week, depending on the activity of the experimental animal. During the training period, 70 dB SPL white noise with a bandwidth of 0.01-50 kHz plays continuously from a central loudspeaker and 200 ms long, 8 kHz, 70 dB SPL pure tone is presented at random times along with the noise. In this method, like the other methods, the animal taught the difference between quiet and noise. It is aimed that when the animal hears sound, suppress the water drinking behavior by foot shock application. The expected performance of the tinnitus-induced animal is the continuation of water drinking behavior even in the silent.

### Lobarinas' Method to Avoid Planned Constructed Polydipsia

In the automatic avoidance technique developed by Lobarinas et al.[29], tinnitus assessment can continue for a long time because behavioral response is not dampened. In the model, polydypsia was induced in food-restricted experimental animals by giving small amounts of food at regular intervals and triggering high water drinking behavior. In the training of drinking behavior with sound, either 30 seconds 40 dB SPL narrowband stimulus or silence condition is randomly applied for 6 trials. In one of the 6 trials, when drinking behavior in the sound condition, the animal is tought to drink water in silence by applying a foot shock. Since the tinnitus-induced experimental animal hears an imaginary sound in the silent interval, it is expected to suppress the drinking behavior as in training.

### Heffner's Sound Localization Method

It was developed to evaluate the presence of tinnitus in experimental animals in which unilateral tinnitus was induced by unilateral noise exposure. Firstly, the experimental animals are conditioned to noise coming from different directions, from the right and left sides of the experimental animal at a 90-degree angle in the cage. The experimental animal is continuously exposed to broadband 35 dB SPL background noise and presented with pure tones 20-30 dB above the hearing threshold at different frequencies. The animal is trained to drink water from a drinking bowl located in the direction of the presented pure tones. Turning to the drinking bowl in the direction of the stimulus is the correct response to the stimulus, while turning to the wrong side is prevented by foot shock as a negative reinforcer. In the experimental phase, although there was no sound in the environment, the experimental animal was expected to perform the auditory condition behaviors on the side of the tinnitus-induced ear[30].

### Physiological Model

Physiological models are based on the measurement of neural activity changes thought to be linked with tinnitus. These measurements are obtained electrophysiologically by recording changes in neural activity directly from the auditory centers of animals exposed to agents that cause tinnitus[31]. In these days, activity changes have been measured by neuroimaging procedures like microPET, fMRI, SPECT, DTI[32,33]. Comparison of data obtained before and after exposure to the substance causing tinnitus, or comparison of results from experimental and control groups, may indicate changes in neural activity. As tinnitus is the perception of sound without external stimulus, the aim of the physiological model is that tinnitus produces normal activities that appear only when there is a sound. The most valid and observable activity is automatic neural firing activity by itself that imitates sound evoked activity. The advantages of the this model that it able to show the characteristics of changes in this activity and its location in the auditory system. On the other hand, the inability to directly prove that animals have tinnitus is the most important negative aspect of this method. Therefore, before using the physiological model, a two-stage evaluation of tinnitus in the animal with a behavioral model can keep the researcher with reliable results[34].

In the physiologic model, tinnitus assessment methods can also be diversified from an audiologic perspective. There are specific electrophysiologic testing methods used in the peripheric and central evaluation of the auditory system. These include the recording of otoacoustic emissions from the outer hair cells, auditory evoked brainstem responses, which allow evaluation of the auditory pathways at the level of the auditory nerve and brainstem, and auditory evoked potentials, which allow evaluation of hearing centers at higher levels near the level of the cortex.

## Conclusion

In conclusion, tinnitus is a symptom whose cause is not fully understood and reduces people's quality of life, and there is no definitive treatment protocol. Although it appears to be a benign symptom, the discomfort caused by the presence of a constant sound in the ears or head can lead to serious psychological problems. The compose of animal models of tinnitus to develop treatment alternatives will continue to be a hope for people suffering from this symptom.

## Ethics

## Footnotes

## Authorship Contributions

Concept: A.A.Y., Design: A.A.Y., Literature Search: B.E.A., A.A.Y., Writing: B.E.A., A.A.Y.

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