

REVIEW ARTICLE

Tinnitus induction in animals and its impact on auditory system structure

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Abstract

Background and Aim: Tinnitus is a perception of sound in ears or head in the absence of any external stimuli. Despite its high prevalence in various age groups, tinnitus has still no effective treatment because its physiological and pathological mechanisms have remained unknown. Since the study of cellular-molecular mechanisms of tinnitus production and stability in human is not feasible, animal models have been used to shed some light on tinnitus induction and propagation mechanisms. This study reviewed some of these research studies. The present review article is based on articles published during 1967–2018 in which keywords such as “salicylate,” “noise,” “tinnitus in the animal model,” and “tinnitus mechanism” were used. These articles were searched in databases such as Science Direct, Google Scholar, PubMed, and Scopus.

Recent Findings: Despite differences in the mechanisms of tinnitus induction, the structural changes initiated from the cochlea and continued to cortex reflect the extent of the affected regions in the creation, development, and preservation of tinnitus.

Conclusion: Animal models (exposed to noise or ototoxic drugs such as salicylate) are ideal tools for studying tinnitus and understanding the details of its propagation and unknown mechanisms.

Keywords: Tinnitus; animal models of tinnitus; salicylate, noise

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Introduction

Tinnitus is the perception of noise in ears or head without any external stimuli. Millions of people hear some noises without any perceptible external source. Tinnitus is not a specific problem of the nervous system, but a clinical symptom in which a series of disorders in internal ear and central auditory pathways are probably involved [1-4]. Tinnitus is now considered a health concern regarding its 8% to 15% prevalence and its disabling outcome in 1% of the population [1,5,6]. Tinnitus involves the auditory and non-auditory structure of the brain, including the limbic system; therefore, it can accompany with disorders such as anxiety, sleep disorders, and emotional disturbance. In severe cases, it can result in depression or even suicide [1,7,8].

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Physiological and pathological mechanisms of tinnitus have remained unknown, and hence, there is no effective treatment for tinnitus [1,3,9-11]. Pseudo-syndromic features of tinnitus are related to vast imaginations of patients with tinnitus. Tonal tinnitus has different pitches in the range of 0.5–16 kHz while non-tonal tinnitus is in the form of buzzing, whistling, hissing, and chirping [3]. Not all types of tinnitus cannot be attributed to specific cause or position which made understanding of its mechanisms more complicated.

Despite the significance of human studies to investigate the involved nervous networks and the relationship between tinnitus features and brain function, the study of cellular-molecular mechanisms of tinnitus production and stability is impossible in human. Therefore, animal models are mainly used to discover some information about the induction and continuation of tinnitus [1,3,9,10].

Animal studies have numerous advantages over human studies among which are direct control of history and reason of tinnitus; wide range of experimental tools, including behavioral and molecular tools; the possibility of using invasive approaches; creation of control and random groups; and finally random evaluation of each member of these groups. To create animal models of tinnitus, they are exposed to noise or chemical treatments which may induce tinnitus in human. In animal models, the animals should be trained to respond in the absence of auditory stimuli or subjective evaluation [2,5,12]. In spite of the progress made in animal studies, there are some limitations, for example, necessity of training and conditioning animals in some methods, uncertainty in the diagnosis of putative tinnitus, lack of evaluation of the emotional components like annoyance of tinnitus, and difficulty in recognizing the emotional reaction to tinnitus [1,5,8,9].

In this review article, we have tried to introduce some of the methods of tinnitus induction in animals, as well as effects of them on the peripheral and central structure of the auditory system, and finally highlighted cellular and molecular mechanisms of tinnitus production in

animal models.

Methods of tinnitus induction

Ototoxic drugs such as sodium salicylate (especially by the production of new and vital drugs) play a crucial role in tinnitus induction. The most common reason for tinnitus is, however, frequent exposure to loud noise. The neural mechanism of noise-induced tinnitus is probably different from those caused by ototoxic drugs [1,13,14]. In this context, various methods of tinnitus induction have been employed in animal studies [10,14]. In continuation, the animal models of tinnitus induction by drugs and the effect of noise on their mechanisms will be discussed.

Sodium salicylate-induced tinnitus

Aspirin belongs to salicylate family which has been widely used in clinical situations for its anti-pain, anti-fever, and anti-inflammatory effects as well as its stroke-preventive role. High doses of salicylate can cause perceptual deficits in human and animal models due to its central and peripheral effects [15-17]. The main impact of high doses of salicylate on the auditory system is the reduction of hearing ability and reversible tinnitus [1,14-16]. Salicylate was used in the first animal models and is now used in most animal models due to its effect in tinnitus induction [10,17]. Depending on salicylate dose, the induced tinnitus is often reversible and at relatively high frequency (10–16 kHz) with mild to moderate temporary changes in threshold; it does not need any clinical intervention [15,18,19]. Numerous studies have shown that the major pathological and pharmacological effects of salicylate on the auditory pathway start from the cochlea and propagate in the central nervous system (CNS). It is believed that the cause of tinnitus is abnormalities in cochlea and changes in the sensory entry from the cochlea to central auditory path [13,15,16]. Most of the cochlear injuries will result in reduced neural output to the neural system. In response to this lack of input, the CNS changes the spontaneous central gain control in different nodes of the central auditory pathway [20], which leads

to variations in intensity encoding [11,21]. Some evidence suggests that salicylate can induce tinnitus through direct influence on target neurons in the auditory system. For instance, in animal models, tinnitus will be induced by diffusion of high concentration of sodium salicylate (1–2 mmol) to the blood brain barrier [15,16]. Tinnitus perception before a sense of hearing loss in human could indicate a higher sensitivity of the brain toward salicylate in comparison with cochlea [13]. Although the minimum effective dose for the induction of tinnitus differs among the animals and its time of administration is also effective, the minimum dose to induce tinnitus in rats is 150 mg/kg [22]. Tinnitus appears in several minutes and reduces 72 hours after the final dose. The high pace of impacts on the cochlea and the central auditory system could be due to the fast entrance of the drug to cochlear perilymph simultaneous to cerebrospinal fluid [13].

Effects of salicylate on the peripheral structure of the auditory system

Sodium salicylate decreases the blood circulation to the cochlea and changes the membrane permeability and the shape of outer hair cells (OHCs). It can also block OHCs' electromotility and hence temporarily reduces the reinforcing effects of cochlea and hearing [14,19]. However, based on the morphological data, salicylate treatment does not cause any apparent damage in hair cells of cochlea or spiral ganglia [18].

Salicylate affects OHC and auditory nerve function which will result in decreased distortion product otoacoustic emission (DPOAE) and compound action potential (CAP), respectively. CAP, however, is being restored to its normal value at the end of treatment [14,17]. Intraperitoneal injection of salicylate (300 mg/kg) in anesthetized rats inhibits DPOAE in high and low frequencies more than in the intermediate ones [13,23]. Moreover, the most sensitive region after salicylate injection was estimated in accordance with tinnitus pitches. In guinea pigs, cochlear microphonic (CM) was not affected by 10 kHz tone after salicylate injection; it,

however, increased in response to 1 kHz tone. Salicylate injection to cochlea also did not influence summing potential (SP) [13].

Effect of salicylate on the central auditory system

Concerning the performance of the central system, salicylate enhances the exciting activity of auditory cortex to harsh noises. This event occurs in spite of the reduction in neural output of cochlea [11]. Salicylate also changes the spontaneous triggering rate and tonotopic organization in the auditory cortex [11,16]. Some neurophysiological studies have shown that high doses of salicylate increase the spontaneous activities of the auditory nerve. However, some studies report that the spontaneous rates of the neurons tuned for low frequencies decrease while the fibers tuned for high frequencies remain unchanged; the exciting activities for maximum noise also remain constant. Such diversity in the results could be due to various animal species studied, different types of anesthetics, duration and the dose of salicylate, evaluation methods, or the type of study (specific cells or subgroups) [16,22].

In the study of Wan et al. on Sprague Dawley rats, the increase in efficiency or accuracy of intensity encoding were not similar for different sounds during tinnitus induction by salicylate. High-frequency tones (especially 15 kHz) showed significant changes in response function, including the increase of saturation level, larger intensity range, and higher slope in comparison with lower frequency tones. This frequency-based effect was in line with high pitch perception of tinnitus in animal models after administration of high doses of salicylate [11]. Furthermore, salicylate disrupts the temporal auditory process in humans with normal hearing ability [13].

Results showed that salicylate affects cochlea and central auditory pathway as well as non-auditory regions of CNS [16]. Imaging and neural physiological evidence support involvement of the central auditory system, prefrontal, and sensory centers in tinnitus. Non-auditory regions such as hippocampus, amygdala, and

cerebellum are also involved in tinnitus; that's why severe tinnitus is often accompanied by stress and depression as well as emotional processing [16,24]. By injecting salicylates in the rats, the relationship between auditory cortex and amygdala and involvement of hippocampus and parahippocampus in animal tinnitus have been proved [25].

Changes in molecular mechanisms as the result of salicylate ototoxicity

Numerous studies have addressed the molecular mechanisms of sodium salicylate ototoxicity [18,26,27]. Salicylate also damages OHC electromotility which may result in hearing loss [14,19] as it acts as a competitive antagonist for chloride anion binding site of prestin (motor protein in OHC) and inhibits OHC motion [13]. Brain imaging after salicylate injection in animals showed enhanced metabolism in central auditory structure and an increase of glucose uptake in the inferior colliculus (IC), auditory cortex (AC), and hippocampus [15,16].

Salicylate excites GABAergic neurons, but its mechanism is unknown. Regarding hyperpolarization of the membrane resting potential, it probably targets ionic channels of the membrane [19,26]. Moreover, regarding the reduced entry resistance of these neurons, salicylate perhaps opens a number of these ionic channels which facilitates the entrance of negative ions or discharge of positive ones. As salicylate decreases the intermediate flow by glycine receptors or GABA_A (gamma-aminobutyric acid A), it may not activate chloride channels; instead, it reinforces potassium ions flow by opening its channels and hemostasis of membrane rest [26,28]. Sodium salicylate also targets metabotropic GABA_A receptors to activate one-way potassium channels to G protein-coupled inwardly-rectifying potassium channel (GIRKs) which hyperpolarizes the resting potential of the membrane and reduces the internal resistance in the rat's medial geniculate body (MGB) [26,29]. Salicylate inhibits cellular cyclooxygenase (COX) activity which will increase intracellular arachidonic acid and prevents its transformation to prostaglandin [14,18]. Increased

level of arachidonic acid affects N-methyl-D-aspartic acid (NMDA) receptors and hence increases spontaneous activities in individual auditory units [14]. Activation of NMDA receptors also influences the rate of synaptic transfer of cochlea. Long-term use of salicylate releases a large number of presynaptic vesicles which may result in larger postsynaptic densities (PSD), longer active synaptic area, and increased synaptic relation to resolving the need for enhanced speed and efficiency of chemical synaptic transfers [16,30]. NMDA receptors are mainly located in PSD neurocytes. Expression of NMDA receptors in the dorsal cochlear nucleus, inferior colliculus, and auditory cortex increases during salicylate-induced tinnitus which may be due to larger PSD [16].

Glutamate-aspartate transporter (GLAST) belongs to glutamate transferase which stabilizes the external environment and maintains intercellular interactions. GLASTs are abundant in the cochlea of Syrian hamster while it is rare in rats and guinea pigs [27,31]. Regarding higher resistance of Syrian hamster to drugs and tinnitus, it was hypothesized that abundance of GLASTs in Syrian rat cochlea can be the reason for such flexibility. In other words, deficiency of GLAST could predict higher sensitivity to noise and drug-induced tinnitus [27].

In animals, tinnitus could be due to the effect of salicylate through activation of pain receptors or transient receptor potential cation channel superfamily V-1 (TRPV1) in the spiral ganglion. TRPV1 is a member of non-selective cation receptor channels which responds to different types of stimuli such as inflammation, heat, and low pH [18,32]. In a study by Kizawa et al., the level of TRPV1 mRNA significantly increased in the spiral ganglion 2 hours after treatment, followed by a significant decrease 12–24 hours after the treatment. It restored to its control level 72 hours after treatment [18]. In animal models, salicylate-induced tinnitus appears 2 hours after injection and disappears 24 hours later [18,32].

Effect of salicylate on neurotransmitters

Sodium salicylate activates serotonergic

neurons (5-HTergic) in the dorsal raphe nucleus (DRN) and increases the serotonin level (5-HT) in IC and AC. Jin et al. study on the optical stimulation of GABAergic neurons in DRN of transgenic Syrian hamster showed that sodium salicylate could increase the excitations of local serotonergic neurons in DRN by inhibiting GABAergic activities. Therefore, it is essential to increase the serotonin level in the brain [26]. Salicylate shows an inhibitory impact on neurologic GABAergic activities in IC and AC. As inhibitory neurons play a vital role in maintaining the excitement level of the central auditory system, a reduction in GABA or glycine inhibition will probably affect the processing in the central auditory system [19]. Salicylate directly changes the performance of inhibitory neurotransmitters which may explain rapid tinnitus induction after salicylate injection [13,19]. Tinnitus-related hyperactivity in the central auditory pathway may be due to reduced inhibition of GABA or increased activity of glutamatergic [16,21]. About 20 to 30% of the neocortex is composed of interstitial neurons most of which are inhibitory and GABAergic ones. The imbalance between stimulation and inhibition in the central auditory system is one of the probable causes of tinnitus which may increase by a reduction in excited flow trigger in interstitial neurons [15,16]. By affecting GABAergic neurons in AC, sodium salicylate influences the glutamatergic and stimulating neurons. By inhibition of interstitial neurons, it overstimulates neural circuits in AC and intensifies synaptic transfer by releasing pyramid neurons [15].

The next neuromodulator involved in plastic variations is nitric oxide (NO) which can be synthesized by nitric oxide enzyme (NOS) and modulate synaptic plasticity to increase or decrease the stimulation. The number of NOS-containing neurons will increase in the ventral cochlear nucleus (VCN) upon induction of transient tinnitus by salicylate [6].

Duration of salicylate administration

Duration of salicylate administration is of crucial importance in the investigation of tinnitus

mechanism. The studies on the central effects of salicylate can be divided into acute and chronic classes. Studies on acute and chronic effects of salicylate can provide some information on different aspects of drug performance in cochlea and brain [13,16]. It is not clear that frequent use of salicylate can induce permanent damages or not. Chronic administration models can be useful in the investigation of tinnitus induction and more permanent injuries in synapses [27]. Generally, acute administration of salicylate will rapidly increase the activities of non-lemniscal pathways while maintaining a constant lemniscal auditory structure. In chronic administration, spontaneous trigger rate will be increased in the lemniscal path [13].

As tinnitus occurs after salicylate injection, investigation of the results in an acute stage of administration in animals is important to determine the affected regions of the brain. Results of chronic administration are however important to study biochemical and neurological mechanisms of tinnitus regulation. For instance, one of the compensating mechanisms is an increase of prestin expression and hence an increase in OHC electromotility which may enhance progressive DPOAE following long-term use of salicylate [13,16]. A single injection of salicylate, however, reduces DPOAE range by decreasing OHC electromotility which is contrary to long-term treatment effects. Therefore, it seems that the response of acute stage of salicylate administration is a transient stress response [14,16].

Noise-induced tinnitus

Exposure to harsh noise is one of the main causes of tinnitus [6,7,33]. In the United States, 3–4 million veterans suffer from tinnitus, and one million of them are searching for proper clinical services. Noise-induced tinnitus can cause high healthcare costs. In the United States, it costs about \$ 2 billion annually [33,34]. Nowadays, in addition to exposure to severe noise in industrial centers, nearly half of teenagers and youth (12–35 years old) are prone to noise-induced problems due to using headphones and personal audio devices [35–38]. In

this context, finding an effective method for the treatment of noise-induced tinnitus is highly essential. But the limitations on understanding the tinnitus mechanisms have hindered achieving these treatments. In the last 15 years, clinical and animal studies have provided valuable information on noise-induced tinnitus [7]. Some animal studies used one-way acoustic trauma with blocking the other ear (by acoustic plaque) to maintain the normal auditory performance of the opposite ear; so the results are not influenced by hearing loss [8,24,39-41]. Some other studies used bilateral acoustic trauma to better estimate the exposure of human to noise [21,33,42]. Acoustic trauma-induced tinnitus is often reported in a tonal form indicating relatively local injury in the central auditory pathway [3].

Effect of noise on the structure of the auditory system

After exposing the animal to acoustic trauma, first, a significant temporary reduction in hearing can be observed which will relatively improve by time and lower permanent threshold reduction remains. Permanent threshold reduction appears in frequencies slightly higher than the frequency of acoustic trauma which is the result of base-oriented injury propagation in inner hair cells (IHC) and OHC of the membrane base [2,43]. This phenomenon is due to nonlinear mechanics of the base membrane which may lead to larger altitude in the base compared to the peak of specific frequency during exposure to high-intensity sounds. It could be the result of base-tended changes in the peak of fluctuations in high intensities or the fact that high-frequency regions are more prone to injuries due to lower antioxidant enzyme activities [43]. Over-stimulation by loud noise can lead to permanent changes in auditory threshold and irreversible damage to stereocilia and hair cells (HCs) destruction which are mainly followed by the destruction of auditory nerve fiber and reduction of spiral ganglion cells [3,43,44]. Damage to synaptic ribbons will probably result in an evident reduction of the fast release of neurotransmitters by IHC to the

nerve, decrease of CAP amplitude, and finally damage to noise intensity coding [38,45]. After an acoustic trauma, the increase of glutamate release from IHCs will cause a reversible inflammation in dendrites of cochlear nerves [3]. Also, toxic excitement of glutamates by over-activities of neurons could destroy peripheral terminals of neurons despite restoring of HCs which may result in their vast destruction [44]. In an active IHC region, about 20 synaptic ribbons exist which collect synaptic vesicles and organize a postsynaptic afferent nerve fiber. By releasing synaptic vesicles, they produce precise and valid spikes [38]. Noise damage to synaptic ribbons of spiral neurons of ganglion and HCs of the cochlea (especially IHCs) is highly reversible, but it won't be reversed entirely [38,45]. For instance, in relatively large rodents (Syrian hamster and guinea pigs) short-term exposure to low-intensity noise (which may not induce permanent hearing loss) could dramatically damage synaptic ribbons. Permanent damage to these synapses will cause the death of spiral neurons of ganglion which were detached from IHCs giving rise to functional deficits in cochlea coding [45]. After noise exposure and by the destruction of cochlear nerve synapses on HCs (similar to the destruction of hair cells of the target), nervous projections do not respond to acoustic stimuli and lose their spontaneous nervous activities. This reduction in nervous activities is probably selective for neurons of the cochlea with a high threshold and low spontaneous discharge rates. Therefore, it can be said that in patients with normal audiograms, tinnitus is accompanied by some sort of peripheral neuropathy [3,44].

Effect of noise on the structure of the central auditory system

It seems that the majority of tinnitus cases is due to noise and accompanied by a reduction of peripheral hearing followed by some variations in central auditory pathways [37,42,43]. Even small changes in sensitivity of cochlea could have a significant impact on the spontaneous triggering rate in the auditory cortex [43,44]. Animal studies have shown that following noise

exposure, increase in spontaneous activity of primary afferent nerve fibers does not remain for a long time, and central hyperactivity phenomena will appear as the result of central plasticity [34,42,43]. In traumatic injuries, brainstem exhibits the highest axonal damage. Despite a limited number of studies, some evidence suggests that axonal changes occur within a week after trauma and vary by the time [34]. One of the reasons of chronic tinnitus is reorganization of auditory cortex (AC) following the cut of peripheral afferent nerve fibers; in other words, chronic tinnitus has the central origin as the sense of imaginary sound remains even after cutting the auditory nerve [2,3,7,37]. Peripheral injuries will increase the threshold in a specific frequency range and decrease the inhibitory entrance of the injured region on neighboring frequencies in the cortex which will result in an increase of spontaneous activities of cortex neurons in vicinity frequencies and their simultaneous activities as well as the extent of central manifestation of these frequencies [2,7,37,44]. In some studies, the increase of spontaneous triggering was proven in some auditory structures such as VCN, DCN, and ICs and AC following noise exposure [7,38,42,43]. It seems that hyperactivity is a reliable indicator of tinnitus [41]. In most cases, hyperacusis was reported in patients with tinnitus, and 86% of them reported hyperacusis along with tinnitus. It could be due to similar mechanisms involved in these two disorders [21].

About 48 to 72 hours after acoustic trauma, a vast microglial activity is observed in CN of rats which may be attributed to inflammatory responses in the central auditory system to create and maintain tinnitus [39]. DCN is an important center involved in the onset and variation of tinnitus since it plays a vital role in the hierarchical process and emergence of tinnitus as the primary acoustic core [41]. Moreover, it is the first place for neural sensory body-auditory integration. In addition to sensory input from auditory neural fibers, DCN receives sensory body inputs from head, neck, upper limb, hands, and feet through triplet nerve and posterior spinal column and transfers them to spindle

shape and gear cell synapses [46]. Long-term sensory-body changes could be an active factor in tinnitus induction as any damage to the auditory nerve could increase sensory-body input and physiologically affect DCN [46,47]. After noise trauma, increase in nerve branching of sensory-body glutamatergic and enhanced sensitivity to their inputs or increased tonic sensory-body inputs are among the main mechanisms in tinnitus [46,48].

In contrast to some studies, Ropp et al. showed that at least 2 months after exposure to noise, DCN role in maintaining tinnitus would fade [40]. Although DCN-induced hyperactivity has been proven in several studies, recent studies, using the same method of tinnitus induction, have suggested that the spontaneous rates of fusiform cells in DCN return to their normal baseline after one to two months (on average: 41 days) [40,49]. If dorsal acoustic stria (which originates from DCN) is discontinued after noise exposure, spontaneous activities in the central division of the inferior colliculus (IC) will decrease which would prevent from tinnitus progress [50,51]. If this strategy is followed a few months later and after stabilization of tinnitus behavior, it will be fruitless. Therefore, DCN transient pathophysiology may be necessary to induce tinnitus, but VCN has a significant role in its sustainability. This means that VCN reorganization and neuronal sustainability are essential for maintaining tinnitus [40].

Coomber et al. have shown that after exposure to noise, spontaneous and bursting neural triggers increases in IC regardless of tinnitus induction. It could be said that increased neural trigger in IC is not a unique indicator of tinnitus and reflects the changes along with mild to moderate hearing loss independent of tinnitus [6]. Moreover, acute acoustic trauma showed no sign of the increase in spontaneous activity in ICC. Two to four weeks later, however, a significant increase is observed in this nucleus which may be attributed to hyperactivity and neural plasticity. The delay in hyperactivity onset could be due to plasticity requirements. This hyperactivity in ICC of the same side or the other one has accompanied with plastic

changes in expression of CN and IC genes. Results showed that the plasticity mechanisms in IC of the same side and the other side are not similar. On the other hand, due to the presence of commissural connections between the two colliculus, same-side hyperactivity could be under the influence of variation in IC of the other side [42]. Furthermore, in another study, no significant changes were observed in DCN, AC, and amygdala after acoustic bursting except demyelination of MGB. As DCN is under the highest direct impact of acoustic trauma (compared to other centers), the reason for this result was not determined. It can be said that bursting will decrease the inputs; then microstructural changes occur in lower regions of the brainstem such as DCN [34]. In addition to various levels of the central auditory pathway, abnormal changes in neural activities have been reported in other regions of the brain which are involved in concentration, memory, and emotion. Acoustic trauma changes the stability of hippocampus cells. These neurons encode the memory of spatial position; hence in patients suffering from tinnitus with hippocampus involvement, the deficits in spatial memory have been also reported [24].

Changes in molecular mechanisms due to noise-induced damages

In auditory fibers, body sensory terminals, and auditory nerve synapses, vesicular glutamate transporters (VGLUTs) are expressed in deep layers of DCN and non-auditory glutamatergic inputs [46,48]. In animal studies, two weeks after a one-sided acoustic trauma, VGLUT₂ increase and VGLUT₁ decrease are observed in the same-side CN [46]. An incremental movement in the sensory-body inputs for granular cells causes a two-sensory increase after exposure to noise. In animal models, the increased expression of VGLUT₂ is associated with overexcitement of neuropathic pain and epileptic seizures, suggesting that the increase in the expression of this receptor in auditory centers may lead to excessive excitement due to tinnitus [46,49]. The two main glutamate transporters called GLAST (often in the cortex and the

hippocampus) and glial glutamate transporter (GLT₁, usually found in the cerebellum) are responsible for absorbing more than 80% of the glutamate in the brain. Shortage of these transmitters is associated with neurotoxic effects in seizures, epilepsy, and probably tinnitus. GLAST exists in astrocytes of the central nervous system, as well as inner phalangeal cells or IPCs (surrounding IHCs and afferent neuron synapses) [27,52]. Since larger changes in hearing threshold and synaptic damages have been detected in GLAST-free Syrian hamster after exposure to noise, it is likely that a part of the resistance of these hamsters to auditory damage is due to higher expression of GLAST in the cochlea of this species [27]. Potassium channel subfamily K member 15 (KCNK15) plays an important role in the regulation of the membrane resting potential and decreasing its expression by increasing the membrane's excitability; this parameter also reduces in IC of the other side two to four weeks after exposure to noise [42].

After acoustic trauma, the regulation of the gene (regardless of their involvement in inhibitory or stimulatory processes) reduces in CN of the same side and on both sides of IC without any change in spontaneous activity of the neurons; this lack of hyperactivity in the acute group is an indication of the superiority of mRNA changes on functional ones [42]. The expression of Arc gene varies in the acute and prolonged changes in the network activity alterations as a result of sensory input changes. Arc mRNA is expressed in the cortex in glutamatergic neurons, and the cortical plasticity is mainly sensitive to Arc surface. Hence its removal will increase the synchronization of the episiotomy-like cortex activity and possibly the tinnitus. For example, the Arc deposition failure in the deprived frequency region can explain the tinnitus pitch. Moreover, Arc excitation in AC, despite a reduction of IHC ribbon (cutting afferent inputs) does not result in tinnitus, but lack of Arc deposition will cause a reduction in ribbons leading to tinnitus [38]. Exposure to explosions will result in tinnitus and hearing loss as well as changes in microstructures. For instance,

changes in myelin and axonal integrity in brain auditory regions (more in IC and MGB), and in cases of traumatic brain damage, reduction of myelin and ischemia have been recorded [34].

Effect of noise on neurotransmitters

Based on various studies, noise-induced tinnitus was associated with changes in inhibitory-stimulatory balance and extensive variations in the expression of genes related to both stimulatory (glutamate) and inhibitory (GABA or glycine) neurotransmitters in CN and ICC of both sides [40-42]. These are accompanied by abnormal hyperactivity of central auditory structure due to stimulation of the peripheral auditory system following noise-induced damage and reduction of GABA and glycine neurotransmitters in the central nucleus [6]. Although numerous studies have discussed increased DCN stimulatory inputs after noise trauma as the reason of hyperactivity, Middleton et al. stated that tinnitus in Syrian hamster was accompanied by DCN hyperactivity due to reduced inhibitory GABA neurotransmitters without any changes in stimulatory ones [41]. Several studies also showed decreased cortical inhibitory as the result of noise exposure as well as faded inhibition after acute acoustic trauma [21]. Moreover, regulation of glycine receptor subunit alpha 1 (GLRA1) inhibitory gene in CN on the same side and IC of the other side decreases two weeks after acoustic trauma. For GABA-A receptor subunit alpha 1 (GABRA1) in IC of the other side, this reduction occurs two to four weeks after trauma. However, some other studies have proven the increase of glutamatergic mechanisms after acoustic trauma and one-sided destruction of the cochlea. Furthermore, an increase is observed in the regulation of GABA-A receptor subunit alpha 1 (GRIN1) (a stimulating one) receptor gene four weeks after noise exposure in CN of the same side which may be involved in the increase of sensitivity [42].

Cochlea excision will result in an increase of NOS in CN neurons. One-sided acoustic trauma will also lead to a significant anti-symmetry in NOS activities among animals with tinnitus. Eight weeks after noise exposure, NOS activity

of the damaged side will increase in comparison with the healthy one which will modulate synaptic plasticity for increase or decrease of stimulation [6,53].

Various studies have reported that auditory stress such as noise exposure may increase the serotonin level in different parts of rat's brain [26,54]. For example, noise exposure changes serotonergic projections to IC. Serotonergic pathways are interacting with tinnitus-involved auditory pathways and can affect the sensory disturbance by modulating these pathways [8,26].

Effects of noise features on tinnitus induction

Due to the use of various noises in animal studies (in terms of intensity, spectrum, and noise duration), the features of the induced tinnitus are different [3]. Noise duration and intensity have a significant role in tinnitus progress as the severity of auditory damage will increase by the enhancement of stimulation intensity and duration [3,55]. For instance, in some studies, 10 ms exposure to burst will involve a wide range of frequencies which are accompanied with early tinnitus onset and central auditory injury in several frequencies (moderate to high range of frequencies) [34]. Wider diversity can be observed for lower noise levels where more time was required for tinnitus emergence [3,13,33]. Increase in the duration of acoustic trauma (while maintaining other features of noise) from 1 to 2 hours will enhance the spontaneous trigger level in IC without any significant change in peripheral threshold [43].

Kiefer et al. used three different bandwidths of noise (0.25, 0.5, and 1 octave around the central frequency of 8 kHz) and studied the nonlinear impacts of these bandwidths on tinnitus induction. Narrow-band noise (0.25 octave) and medium-band noise (0.5 octave) were associated with a higher risk of tinnitus compared with the wide-band noise (1 octave). The strongest effect in terms of test frequency numbers and the number of animals with tinnitus was observed in medium-band noise. For all three mentioned noise bands, frequency-dependent distribution of induced tinnitus is more tended

to the high-frequency noise, and it has two peaks. For narrow and medium band noises, one peak can be seen around and above the trauma frequency while the second one is located at high-frequency range (14–20 kHz) with a slope around 12 kHz. In the case of wide-band noise, two frequency ranges are observed: low (4 and 6 kHz) and high (16 kHz) [3].

In most of the cases, tinnitus frequency was reported one octave above the hearing loss region which indicates the general pattern of tinnitus [34]. Moreover, the increase in spontaneous trigger rate is not observed in all frequency ranges but instead reported in neurons with intermediate frequencies near or above noise frequency [3,42,43]. In some studies, if the temporary reduction in threshold is created by pure tone, tinnitus pitch corresponds to an upper frequency of maximum hearing loss (sometimes 0.5 octave). On the contrary, when temporary hearing loss is created by one noise of octave band or 1/3 octave, tinnitus pitch will be understood below the frequency of maximum hearing loss [43,56,57]. Moreover, it seems that variation in noise-induced threshold after noise trauma is independent of noise band and changes in the thresholds are completed eight weeks after exposure to medium-band noise indicating that although bandwidth of the acoustic trauma affects cochlea, it can be discovered in the long term [3].

Effect of noise with aging

Owing to the short lifetime of the mice (about two years) and a possibility to use age-accelerating models in these animals (i.e. age-dependent hearing loss in C57BL/6J and 129S2/SvPas mice), they are ideal models for investigating the behavioral symptoms of tinnitus after noise exposure and extending these changes by passing of time. Hence they can be used to study the interactions between aging and tinnitus which may help understand details of tinnitus progress and aging in pathways which have not been understood yet [2].

From the clinical point of view, tinnitus prevalence increases by aging. On the other hand, exposure to noise will increase the chance of

tinnitus [10,58]. Similar to hearing loss, tinnitus can emerge years after noise exposure, for instance, veterans are more prone to tinnitus than normal people (more than twice), and the highest difference can be observed in the age range of 50–70 years [2,59]. Most people report their first experience of tinnitus in the middle or late adulthood which is probably induced after primary noise trauma in combination with aging [2]. Based on medical jurisprudence findings, although noise-induced tinnitus sometimes appears suddenly, a majority of cases appear gradually and in relation with hearing loss and progress to the point that cannot be ignored anymore [2,60].

Conclusion

Since the establishment of a behavioral model of noise-induced tinnitus in rats by Jastreboff, drugs have been used in various species to investigate the biological mechanism of tinnitus induction [13]. Salicylate is the most common drug used in animal models to induce tinnitus and has several advantages over severe noise exposure. Some advantages are the possibility of its use to induce tinnitus in the human model; rapid and reversible tinnitus induction; administered as oral drug or injection; investigating physiological changes, before, during, and after tinnitus; and finally salicylate is a valid method to induce transient tinnitus in animals with lower changes in comparison with noise exposure and in a shorter time interval (5 hours in comparison with 8 weeks) [1,13,27]. On the other hand, one of the limitations of tinnitus induction by salicylate is that it induces bilateral hearing loss and tinnitus in both ears. Acoustic trauma, however, could cause one-ear or bilateral tinnitus; hence it can provide the opportunity to investigate the tinnitus-relevant changes in the same ear or the other one [13].

Distinct cochlea differences can be observed between salicylate- and noise-induced tinnitus; the spontaneous activity of auditory nerve increases after salicylate administration, but it decreases following noise exposure [27]. As most of the measurements have been carried out after noise exposure and not during that, the

initial phase of increased auditory nerve activity during noise exposure and its decrease due to permanent synaptic damage after noise exposure are probably [13,27]. Unlike noise exposure, the animals will be investigated shortly after the injection when maximum salicylate can be found in the cochlea [27]. Therefore, the difference in the results of these two methods can be attributed to that. Regarding what mentioned in the previous sections, it can be said that despite differences in mechanisms of tinnitus induction, structural changes in both methods initiated from the cochlea and continued to cortex reflecting the extent of the involved regions in the creation, development, and preservation of tinnitus.

Conflict of interest

The authors declared no conflicts of interest.

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