Review

The Pathophysiologic Mechanism of Tinnitus

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Tinnitus represents a phantom auditory sensation without an external sound source. The reported prevalence of tinnitus estimates 15-20% in world population. Although severe tinnitus might be associated with deterioration of quality of life, depression and anxiety, treatment modalities of tinnitus have not been established yet. Considering the heterogeneity of tinnitus, a single theory or a hypothesis cannot sufficiently explain the mechanism of tinnitus. Thus, diverse theories and studies had been conducted to elucidate the secret of tinnitus. Degeneration of outer hair cell in the peripheral auditory system is known to be associated with tinnitus, while auditory plasticity theory, upregulation of excitation of central auditory structures explains the role of the central auditory pathway in the generation of tinnitus. In addition, somatosensory and limbic autonomic nervous systems are also deeply involved with the pathogenesis of tinnitus. Herein, recent pathophysiologic theories and remarkable studies of tinnitus were reviewed. Understanding of the mechanism of the tinnitus generation might be the cornerstone in the development of tinnitus treatment.

Key Words: Tinnitus; Pathophysiology; Mechanism

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INTRODUCTION

Tinnitus is defined as a phantom auditory perception in the absence of a corresponding external sound source [1]. Tinnitus is a common condition in the Otolaryngology field and is a global public health concern affecting the quality of life and psychological health. A recent nationwide survey demonstrated that the prevalence of any tinnitus in South Korea was 19.7% and among those with any tinnitus, 29.3% experienced annoying tinnitus affecting daily life [2]. It is estimated that approximately 15-20% of the world population suffer from tinnitus [3,4]. Severe tinnitus is frequently associated with depression, anxiety, insomnia, and suicidal attempt [5]. The prevalence of tinnitus increases with age and presence of hearing loss [2].

Although a number of theories for the etiology of tinnitus were proposed, a single theory or a hypothesis could not explain the mechanism due to the diverse nature of tinnitus.

Tinnitus can be divided into subjective/sensorineural tinnitus and objective/somatic tinnitus. Objective tinnitus refers to somatic sounds perceived as tinnitus that can be produced by musculoskeletal or vascular problems. Objective tinnitus can be heard by someone else by stethoscope and is easily distinguished from sensorineural tinnitus by its typical pulsatile or repetitive sound with or without synchronization with the heartbeat. The causes of objective tinnitus were venous hum, high jugular bulb, A-V malformation, middle ear myoclonus and palatal myoclonus, etc., those are easily identifiable with examination. However, most tinnitus patients suffer with sensorineural tinnitus that might be caused by damage at the level of the cochlea or alternation of the central auditory pathway. Sensorineural tinnitus can be expressed as tonal sound, narrow band sound or white noise. Subjective tinnitus can only be heard by the affected person. Most frequent causes of subjective tinnitus is noise induced hearing loss which destruct the hair cells in the inner ear. In addition, a recent study revealed that tinnitus is a consequence of neuroplastic alterations in the central auditory pathway as well as somatosensory change. However, the exact mechanism of subjective tinnitus is obscure.

In this review, the author focuses on the etiologic background

and pathophysiology of subjective tinnitus and discusses the widely known theories that explain the generation of subjective tinnitus.

UNDERLYING CONDITIONS OF TINNITUS

Tinnitus can be caused by various underlying conditions because it is a symptom rather than a disease entity [6]. Any otologic disease can generate sensorineural tinnitus, common causes include presbycusis, noise induced hearing loss, Meniere's disease, sudden sensorineural hearing loss and conductive hearing loss, etc. Central nervous system problems such as head trauma, stroke, multiple sclerosis, cerebellopontine angle tumor, autoimmune inner ear disease, rheumatoid arthritis, and systemic lupus erythematosus can also cause tinnitus. In addition, cochlear damage following use of salicylate, antibiotics, loop diuretics or platinum based chemotherapeutic agents can generate tinnitus. Infectious causes of tinnitus include Rubella, neurosyphilis, Lyme disease, Measles, meningitis and chronic otitis media. Among various causative diseases, hearing loss following the excessive noise exposure is the most common etiology for tinnitus [7]. Accordingly, any disease causing hearing loss might be associated with the generation of tinnitus and type of hearing loss (sensorineural or conductive) might not impact on the etiology of tinnitus. Moreover, tinnitus can also develop in the subjects with normal hearing level [8]. Likewise, tinnitus represents a symptom of diverse pathologies. Research on tinnitus etiology has been focused on peripheral and central auditory pathway.

ANIMAL MODELS OF TINNITUS: BEHAVIORAL AND PHYSIOLOGICAL MODELS

The attempts to elucidate the tinnitus mechanism have been conducted in various ways. Tinnitus animal model can indirectly show the substantial change of the auditory pathway in accordance to tinnitus [9]. Animal models of tinnitus were divided into two general categories, behavioral models and physiological models.

Behavioral models were designed for the measurement of tinnitus percepts in animals. These models allow examination of the psychophysical attributes of tinnitus, including pitch, loudness and the time course of tinnitus. Behavioral model based on an "acoustic startle reflex test" provided a turning point of tinnitus research by reducing the test time and increasing test reliability [10].

Physiological models concerns the changes in the auditory pathway influenced by tinnitus. The aims of these models were to identify, localize and measure the signals at the neuronal level that lead to tinnitus perception and explain the mechanisms by which such signals are triggered. Direct recording of electrophysiological parameters or neuroimaging techniques were used to identify the changes of neural activity in selected areas of animals treated by an agent which generates tinnitus [11]. These models provided important insight into the location and characteristics of defects underlying tinnitus, by showing increases in spontaneous activity in dorsal cochlear nucleus, inferior colliculus and primary auditory cortex, and increased neural synchrony and bursting activity in the auditory pathway [12,13].

SPONTANEOUS OTOACOUSTIC EMISSIONS

Normal healthy cochlea can produce sound in the absence of any acoustic stimulation. Low intensity tonal or narrow band sound is supposed to be generated in the course of the active process of the outer hair cell which has electro-motile activity. The spontaneous sound generated in the cochlea was firstly detected in the external auditory canal by Kemp and the SOAE is considered to be one source of tinnitus, so called cochlear mechanical tinnitus [14]. This form of tinnitus is mild and likely to be found in the normal hearing population and subjects with middle-ear diseases. However, 38-60% of normal hearing adults have measurable SOAEs and most of the subjects with SOAE are not aware of tinnitus. Other research showed that SOAEs are rarely detected in tinnitus patients and SOAE could not be identified in case of hearing thresholds over 35 dB [15]. An experimental study postulated the dissociation of SAOEs and tinnitus showing that salicylate largely abolished SOAE without decrement of tinnitus perception [13]. Likewise, the mechanism of tinnitus could not be fully explained by the presence of SOAEs.

DISCORDANT DAMAGE OF HAIR CELLS

Organ of Corti is the receptor organ located in the cochlea. It consists of hair cells, basilar membrane, tectorial membrane and supporting cells that allow auditory transduction, which changes auditory signals to electrical signals. Inner hair cells (IHC) are receptor cells for sound transduction and most afferent neurons (type 1 neuron) innervate IHCs. Outer hair cells (OHC) are

thought to amplify sound through an active vibration of a cell body, so called electro motility. These active process of OHCs have a significant role as a cochlear amplifier by adding up to 50 dB and OHC have an ability to control the sensitivity of IHCs by setting the operating point of the IHCs' transfer characteristic [16]. Previous experiments showed that OHCs are more vulnerable to noise and ototoxic agent than IHC [17]. In a partially damaged cochlea, there should be an area of both OHCs and IHCs damaged; an area with OHCs damaged, but IHCs are intact; and an area with both OHCs and IHCs intact. In the area with damaged OHCs and intact IHCs, the decoupling between the tectorial membrane and cilia of OHC might disturb the normal damping properties of OHC, so that the tectorial membrane might directly impinge only upon the cilia of IHCs, causing IHCs to depolarize more. Increase afferent input from IHCs might play a significant role in the generation of tinnitus. In addition, a loss of motility in OHCs might reduce the ability to set the sensitivity of the IHCs causing a 'virtual' sound input, so that this normally inaudible activity might be perceived as tinnitus [18].

In another example of where IHC damage was present, decreased IHC afferent input area might cause the reduced efferent inhibition of OHCs. But as one efferent nerve innervate many (20-30) OHCs, the normal IHCs that are innervated with some efferent fibers with damaged IHCs nearby also have reduced efferent inhibition, resulting in tonal tinnitus [19].

BIOCHEMICAL MODEL OF INNER HAIR CELLS

The IHCs have been the focus of several models of tinnitus because they play a major role in afferent neurotransmission. One hypothesis postulated that alterations in hair cell physiology are the triggering mechanisms of tinnitus induction. Increases in ion permeability caused by hair cell damage, might trigger an increased glutamate release from the presynaptic ending of the IHCs leading to hyper-activation of auditory nerves. Another model demonstrated that endogenous dynorphins possibly potentiate the excitatory properties of glutamate in IHCs in response to stimuli or in silence [20]. Glutamate induced excitotoxicity could be identified as an altered neural excitability and altered discharge spectrum in type I neuron normally characterized by low rates of spontaneous discharge and poorly defined threshold.

AUDITORY NERVE

Neurovascular compression in cranial nerve is a frequent cause of trigeminal neuralgia, hemi-facial spasm, and recurrent vertigo. Arteries elongate and the brain sags with age, redundant arterial loops or intrinsic hindbrain veins may cause cross compression of the cranial nerve entry zone in the cerebellopontine angle [21]. Tinnitus is also caused by neurovascular compression of the 8th nerve. Although the influences of vascular compression on the generation of tinnitus are unclear, neurovascular decompression resulted in 40% improvement of tinnitus in the patients after surgery [22]. Vascular compression theory can be explained by the loss of excitatory input, which might release certain neuron form inhibitory signals, causing them to become hyperactive enough to generate tinnitus. Interestingly, vascular decompression has favorable effects in patients with acute tinnitus, while many patients with chronic tinnitus did not benefit from surgical decompression. In addition, tinnitus has been sustained in those patients where their auditory nerve had been surgically dissected due to acoustic neuroma [23]. Based on these observations, tinnitus by compression of auditory nerve might trigger plastic reorganization of the central auditory pathway [13].

DORSAL COCHLEAR NUCLEUS

The dorsal cochlear nucleus (DCN), a brainstem nucleus that receives direct input from the auditory nerve, is a key structure for the generation of tinnitus [24]. After noise exposure, increased spontaneous firing rates were detected in Fusiform cells, the principal output neurons of the DCN and psychophysical evidence of tinnitus was identified simultaneously [25]. It is postulated that a decreased auditory nerve input leads to disinhibition of the DCN and an increase in spontaneous activity in the central auditory system related to tinnitus generation [26]. OHC damage also triggers plastic readjustments of the DCN and lead to tinnitus with a delayed onset [6].

MALADAPTIVE PLASTICITY

Tinnitus is frequently associated with hearing loss. Decreased input from the cochlea to the central auditory pathways triggers plastic neural changes that result in increased spontaneous activity and synchrony in affected regions. However, neurons in non-

auditory regions also could be influenced by tinnitus. Animal studies have identified tinnitus-associated neural changes which start at the cochlear nucleus and extend to the auditory cortex and other brain regions. The hypothesis of maladaptive neural plasticity seems to explain those changes of increased spontaneous firing rates and synchrony among neurons in central auditory structures and non-auditory brain networks, possibly generating the phantom percept analogue to phantom limb sensation [27].

Animal studies have shown that integration of auditory and somatosensory afferent neurons takes place in the DCN, where afferent neurons from the auditory nerve, trigeminal nerve, dorsal column ganglia, and brain stem nuclei converge [28]. After cochlear damage decreases auditory nerve input to the cochlear nucleus, somatosensory inputs to the cochlear nucleus are upregulated for a few days, resulting in increased fusiform cell responses to somatosensory stimulation. This mechanism was probably caused by the increased non-auditory glutamatergic innervation after cochlear damage and the fusiform cells in the DCN are responsible for multisensory integration via stimulus-timing-dependent long-term plasticity [29].

A lot of research has revealed the tinnitus-related changes in non-auditory brain areas showing structural and functional alterations in the prefrontal cortex, parietal cortex, cingulate cortex, amygdala, hippocampus, nucleus accumbens, insula, thalamus, and cerebellum [30,31]. Although it is difficult to specify the tinnitus related brain changes considering the effect of other frequent comorbidities of hearing loss, hyperacusis and distress behavior, neuroimaging studies of tinnitus-related changes in brain structure and studies about functional connectivity between brain regions have been extensively investigated. The parahippocampal region, which is associated with memory was the consistently highlighted area in the brain with functional imaging studies [31,32]. In patients with tinnitus, the parahipoccampal region showed increased connections to the auditory cortex in resting-state EEG or fMRI studies [31]. Those findings might support the hypothesis that auditory perception is based on predictions about the external world that require information about the one's history with sound. Other brain areas showing increased activation in tinnitus patients are the anterior cingulate cortex (ACC) and insula [33,34]. Because these two areas are main regions of the 'salience', increased activity in the ACC and the insula may imply the association of salience to the tinnitus sound [35].

SOMATOSENSORY SYSTEM

Tinnitus patients frequently experienced the change of pitch or loudness of their tinnitus, according to teeth clenching, pressure on the forehead, occiput or vertex, shoulder movement or head movement [36]. A hypothesis that somatosensory input can modulate tinnitus, has been postulated by showing the interaction between auditory perception and somatosensory input in the DCN. The anatomical links between the DCN and somatosensory nuclei, located in the medulla receive afferent neurons of cranial nerve V, VII, IX, and X, might provide a basis for somatosensory modulation of tinnitus [37]. Levine hypothesized that decreases in inhibitory somatosensory nuclei input to the DCN might result in disinhibition of DCN activity leading to increased perception of tinnitus [36]. Although the anatomical connection between DCN and medullary somatosensory nuclei have been identified in the cat, uncertain anatomical links in humans are a weak point of the hypothesis.

NEUROPHYSIOLOGICAL MODEL OF TINNITUS

In the neurophysiological perspective, the role of neural network in the generation of tinnitus had been emphasized. The neurophysiological model devised by Jastreboff, suggested that tinnitus is linked with auditory perceptual, emotional and reactive systems. Accordingly, the habituation process might reduce or eliminate prolonged tinnitus perception against a brief span of tinnitus related activity, while the negative emotional reinforcement by the limbic system and autonomic activation might enhance the perception of tinnitus. Thus, interactions of tinnitus perception, behavioral/emotional reaction and autonomic response can worsen the perception of tinnitus making a positive feedback loop [38]. The neurophysiological model has been widely accepted in this field and habituation strategy to both tinnitus signal and the reaction against tinnitus has been developed as a Tinnitus Retraining Therapy [39].

CONCLUSION

Tinnitus is a prevalent and intriguing symptom that can be caused by various diseases. Recent research on neurophysiology and tinnitus models expanded the basic understanding of tinnitus. The complex interaction between peripheral auditory path-

ways, central auditory pathway and non-auditory region of the limbic, somatosensory and autonomic system, might contribute to the generation and persistence of tinnitus. An accumulation of knowledge of fundamental mechanism might help to develop novel treatments and prevention modalities for tinnitus.

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