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Review

Subjective tinnitus: lesion-induced pathological central homeostasis remodeling

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ABSTRACT

Subjective tinnitus is the most common type of tinnitus, which is the manifestation of pathological activities in the brain. It happens in a substantial portion of the general population and brings significant burden to the society. Severe subjective tinnitus can lead to depression and insomnia and severely affects patients' quality of life. However, due to poor understanding of its etiology and pathogenesis, treatment of subjective tinnitus remains challenging. In recent decades, a growing number of studies have shown that subjective tinnitus is related to lesion-induced neural plasticity of auditory and non-auditory central systems. This article reviews cellular mechanisms of neural plasticity in subjective tinnitus to provide further understanding of its pathogenesis.

Contents

1. Introduction

Subjective tinnitus is the manifestation of pathological activities in the brain. It is reported that the prevalence of subjective tinnitus ranges from 7.5% to 60% in children (Krog et al., 2010), about 4.7% in the youth population (Langguth et al., 2013), and reaches a peak of 14.3% between the ages of 60 and 69 years (De Ridder et al., 2007). Patients with severe subjective tinnitus account for 1–2% of the

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total population (Langguth et al., 2013), among whom about 50% suffer from depression and 40% suffer from insomnia (Phoon et al., 1993; De Ridder et al., 2007). At the same time, the social burden of subjective tinnitus is enormous. According to a 2013 Dutch study, the average medical cost of tinnitus is 1.9 billion euro per year (Maes et al., 2013). However, due to insufficient understanding of its etiology and pathophysiology, treatment of subjective tinnitus remains challenging.

In recent decades, a variety of neurophysiological hypotheses have been proposed to elucidate the underlying mechanism of subjective tinnitus, including tonotopic reorganization (Van Dijk and Langers, 2013), neurosynchrony enhancement (Fuglsang et al., 2020), spontaneous hyperactivity (Salvi et al., 1990; Zhang et al., 2006), thalamocortical dysrhythmia (De Ridder et al., 2015), abnormal filtering in limbic areas (Rauschecker et al., 2010; Leaver et al., 2011), auditory-somatosensory plasticity disorder (Shore et al., 2016), origin of cerebellum (Bauer et al., 2013), etc. These hypotheses analyze the pathogenesis of tinnitus from different perspectives. However, in fact, as Shulman et al. proposed (Shulman, 1995; Shulman et al., 2009), a final common pathway may exist for all patients with subjective tinnitus, despite different causes. Based on the latest progress in tinnitus research, this paper discusses the cellular mechanism of neural plasticity in subjective tinnitus. For convenience, tinnitus is used to refer to subjective tinnitus in this review.

2. Etiology

People with normal hearing can perceive tinnitus in a sound isolation booth, although they do not feel it in quiet (Turrigiano and Nelson, 2004; Norena, 2011). It is suggested that in a quiet environment, the low level of sound pressure can still drive inner hair cells (IHC) to release excitatory neurotransmitters into the ribbon synaptic cleft, thus keeping the activity of the auditory nerve (AN) within its normal working range. However, in a sound isolation room, where sound pressure is almost cancelled, the working range of AN activity cannot be maintained, resulting in insufficient auditory input into higher level auditory centers, which may then present pathological activities that can be perceived as tinnitus by the cognitive center. This phenomenon suggests that insufficient auditory input may be an important factor causing tinnitus.

Damage to the auditory pathway can seriously reduce auditory input and cause tinnitus. It has been reported that damage of the peripheral auditory pathway, such as cochlear lesions (Kaltenbach and McCaslin, 1996), vestibular schwannoma (VS) (Bell et al., 2016) or auditory nerve transection (House and Brackmann, 1981), can lead to tinnitus. Corresponding to decreased peripheral auditory input, central lesions impairing central auditory pathways, such as hemorrhage in the lateral lemniscus (LL) (Cho et al., 2005), inferior colliculus (IC) (Stimmer et al., 2009), cerebellum (Matsuda et al., 1993) and primary auditory cortex (A1) (Yoneoka et al., 2001), can also cause tinnitus. Tinnitus caused by reduced auditory input can be called hearing loss related tinnitus. Hearing loss related tinnitus caused by peripheral auditory system impairment can be called peripheral drive tinnitus, while hearing loss related tinnitus caused by central lesions can be called central drive tinnitus (Table 1).

3. Origin

The origin of tinnitus may be different from its driving positions. Multiple studies have demonstrated hyperactivity in projection neurons at multiple centers in the auditory system in animal models after noise exposure, including the dorsal cochlear nucleus (DCN) (Finlayson and Kaltenbach, 2009; Pilati et al., 2012; Criddle et al., 2018), ventral cochlear nucleus (VCN) (Vogler et al., 2011), IC (Szczepaniak and Møller, 1995) and auditory cortex (AC) (Norena, 2011; Auerbach et al., 2014). Human neurophysiological and functional imaging studies have also visualized various regions of hyperactivity in the auditory pathways and nonauditory brain structures in tinnitus patients (Rauschecker et al., 2010; Leaver et al., 2011). Here, we will discuss, among these hyperreactive zones after noise damage, which level is the most relevant to the generation of tinnitus based on recent researches.

3.1. Cochlear nucleus (CN)

The mammalian cochlear nucleus (CN) is the lowest central auditory nucleus in the auditory pathway, which is divided into two parts: VCN and DCN. VCN is the first projection center of the ascending auditory pathway in mammalian brainstem. It receives direct auditory input from the AN and transmits auditory information to advanced auditory centers (Vogler et al., 2011). DCN is also an important subdivision of mammalian CN. Previous studies had revealed that DCN is involved in sound localization and feature extraction of sound stimuli (Mao et al., 2015).

In anesthetized animal models of tinnitus, almost all VCN activity disappeared immediately after noise exposure, following similar changes in the AN (Koerber et al., 1966). Following this rapid activity reduction was a chronic increase in spontaneous discharge in the VCN (Vogler et al., 2011). Different from the VCN, after noise exposure, the DCN showed relatively unaffected activity initially, although followed by rapid and significantly enhanced evoked responses (DCN-ER) (Middleton et al., 2011) and then chronically enhanced spontaneous discharge in fusiform cells (Kaltenbach and McCaslin, 1996; Pilati et al., 2012). This indicates that DCN has biphasic rapid and chronic hyperactivities in response to reduced auditory input (Koerber et al., 1966). Loss of stimulus-driven activity may cause disinhibition or compensatory enhancement of spontaneous discharge of DCN fusiform cells. However, it had been reported that bilateral DCN ablation did not eliminate tinnitus (Brozoski and Bauer, 2005), although some studies had also showed that DCN ablation before noise damage could prevent tinnitus (Brozoski et al., 2012). These studies suggest that DCN may not be the origin of tinnitus, but may be related to tinnitus driving process.

The activity in VCN was normally controlled by the AN (Koerber et al., 1966). When the VCN lost stimulation from the AN due to its significantly reduced activity, it presented chronically enhanced discharge (Vogler et al., 2011). As fusiform cells are the only output cells of the DCN and connect with the VCN, the chronically enhanced VCN discharge post reduced input may be caused by these DCN fusiform cells.

3.2. Inferior colliculus (IC)

The inferior colliculus (IC) is a midbrain structure that integrates most of the ascending auditory information and projects it to the AC through the thalamus. Previous studies on tinnitus mainly focused on the role of IC in the origin of tinnitus (Mulders and Robertson, 2013; Berger and Coomber, 2015). However, the results showed that auditory evoked responses of the IC (IC-ER) rapidly decreased (Popelár et al., 1987), while the spontaneous discharge of IC slowly increased (Robertson et al., 2013) after noise exposure in animal model of tinnitus, suggesting similar changes in the IC as in the VCN. It was also reported that ablation of DCN significantly reduced chronically increased spontaneous discharge in the IC (Manzoor et al., 2012), suggesting that enhancement of spontaneous discharge in the IC after noise exposure was also caused by the relay of DCN, similar with VCN. It appears that chronically enhanced activity in both VCN and IC following noise

Table 1
Classification of hearing-loss tinnitus and selected examples.

Hearing-loss Tinnitus	Examples
Peripheral drive tinnitus	Conductive hearing loss
	Sensorineural hearing loss
	Endolymphatic hydrops (Meniere disease)
	Third window anomalies (SSCD)
	Tumors (vestibular schwannomas, meningiomas)
Central drive tinnitus	Hemorrhage (lateral lemniscus, cerebellum, primary auditory cortex, etc)
	Ischemia
	Tumors (glioma, metastatic tumor, etc)
	Brain abscess

exposure may originate from DCN fuciform cells, although further studies are needed to confirm this deduction.

3.3. Auditory cortex (AC)

The auditory cortex (AC) is part of the temporal cortex. AC is located at the junction of auditory up-down pathway and higher-order cognitive centers, and provides central processing that transforms auditory signals into perceptual representation. After noise trauma, evoked responses in the AC (AC-ER) were significantly enhanced in conscious animals (Popelár et al., 1987; Sun et al., 2012) and spontaneous neural activities in the AC increased gradually (Eggermont and Komiya, 2000; Seki and Eggermont, 2003), suggesting a biphasic rapid and slow hyperactivity in the AC following noise trauma similar to the reaction characteristics in the DCN. It was also reported that knockout of the GABA synthase (GAD65) gene in the AC could cause tinnitus in normal hearing mice (Miyakawa et al., 2019), while GABA enhancing drugs in A1 could eliminate tinnitus in hearing impaired rats (Yang et al., 2011). These studies suggest that changes at the cortical level may be the key in tinnitus generation.

3.4. Non-auditory system

Imaging studies have demonstrated activation of non-auditory central systems, especially the limbic system in tinnitus patients (Rauschecker et al., 2010; Leaver et al., 2011). However, it remains unclear whether these non-auditory circuits are related to tinnitus perception, or merely to problems related to tinnitus, such as distress at the time. Although modulation of tinnitus intensity by non-auditory factors is well known in chronic tinnitus, it is the failure of the limbic regions to block this signal that leads to tinnitus (Rauschecker et al., 2010).

In summary, previous studies showed biphasic rapid and chronic hyperactivity post noise trauma in animal models of tinnitus in both DCN (Middleton et al., 2011; Pilati et al., 2012) and AC (Popelár et al., 1987; Qiu et al., 2000), although ablation of DCN did not eliminate tinnitus (Brozoski and Bauer, 2005). Frequency-specific reorganization caused by cochlear lesions was only found in the AC and thalamus, but not in other peripheral stations in cats and monkeys (Heil et al., 1994; Irvine et al., 2000). GAD65 gene knockout in the AC caused tinnitus in normal hearing mice (Miyakawa et al., 2019), and GABA enhancing drugs in A1 eliminated tinnitus in hearing impaired rats (Yang et al., 2011). These results suggest that neural plasticity in the AC may be closely related to the generation of tinnitus, and the DCN may play an important role in the driving process of tinnitus. Therefore, it is of great significance to further study the role of AC in tinnitus and its molecular mechanisms.

4. Pathogenesis

The sensory system of almost all organisms involves the input of sensory stimulation and the output of behavioral response (Shulman, 1995). The loss of sensory input caused by diseases leads to compensatory elevation of spontaneous discharge of pyramidal projection neurons regulated by the central firing rate homeostasis mechanism (Eggermont and Roberts, 2004; Florence and Kaas, 1995; Schmid et al., 1995). Lesion-induced central plasticity has been documented in the auditory system (Middleton et al., 2011; Pilati et al., 2012; Norena, 2011; Auerbach et al., 2014), somatosensory system (Florence and Kaas, 1995; Fernández-López et al., 2019), visual system (Schmid et al., 1995; Keck T et al., 2013), etc. Over the past 20 years, more and more researches have shown that subjective tinnitus is caused by lesion-induced central plasticity in the auditory system, that is, the rebalance of central firing rate homeostasis due to auditory deprivation (Eggermont and Roberts, 2004; Roberts et al., 2010).

4.1. Central firing rate homeostasis

The concept of homeostasis was first proposed by Cannon in 1932 (Burrone and Murthy, 2003). Homeostatic mechanism is responsible for maintaining the stability of biological systems, which may be the result of millions of years of evolution in mammals (Schulz, 2006; Fjeld et al., 2017). In the CNS, homeostatic mechanism maintains firing rates of excitatory neurons in an optimal working range despite dynamically changing input (Walmsley et al., 2006; Bishop and Zito, 2013). There are two main regulation modes responsible for central firing rate homeostasis in vivo: presynaptic and postsyantic homeostatic plasticity (Turrigiano, 2008; Delvendahl and Muller, 2019). Presynaptic homeostatic plasticity (PHP) regulates the release of presynaptic neurotransmitters and mediates short-term synaptic plasticity on a time scale of milliseconds to seconds (Zucker and Regehr, 2002; Davis and Muller, 2015). Postsynaptic plasticity mediates long-term synaptic plasticity at an hour-to-day time scale by regulating the number of postsynaptic neurotransmitter receptors (Shepherd et al., 2006; Turrigiano, 2008). Presynaptic and postsynaptic homeostatic plasticity may present fast and slow phase responses respectively to maintain the stability of the CNS.

Both patterns of central firing rate homeostasis are controlled by negative feedback regulation (NFR) of cortical GABAergic interneurons (Mann and Paulsen, 2006; Xue et al., 2011), which may be the homeostatic regulating circuit for all sensory pathways (Fig. 1). The neural network of the mammalian cortex consists of two types of neurons: excitatory neurons (i.e. pyramidal neurons) and inhibitory neurons (i.e. GABAergic interneurons). The activity of pyramidal neurons is controlled by GABAergic interneurons through GABA receptors (GABAR) located on their presynaptic and postsynaptic membranes (Maffei and Fontanini, 2009; Xue et al.,

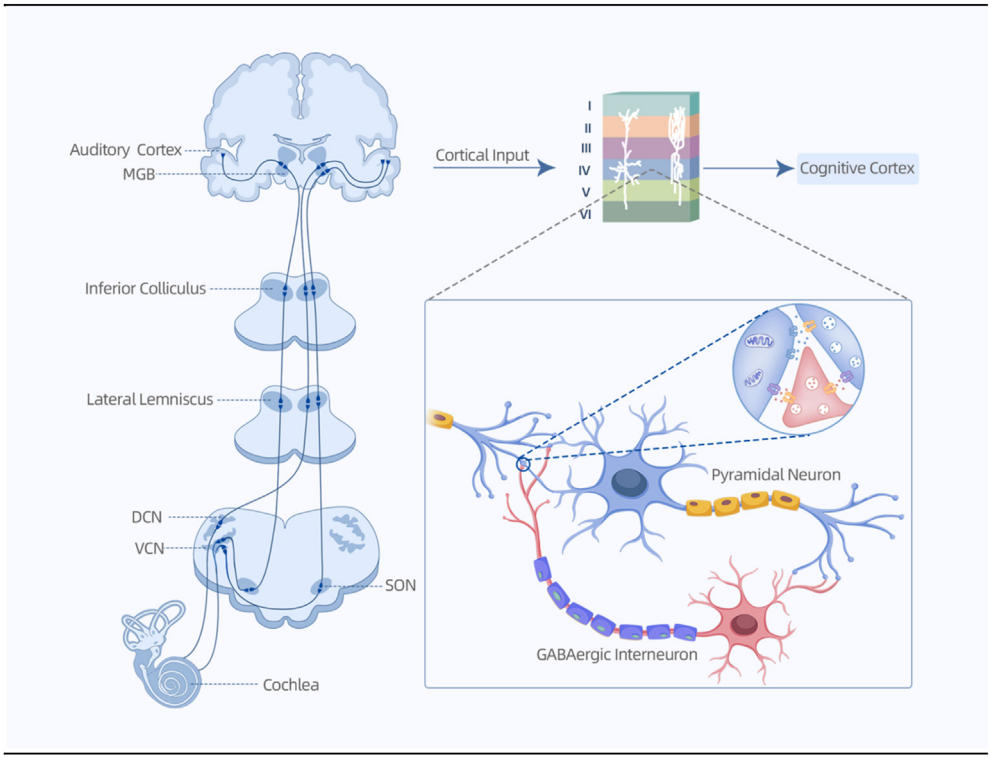

Fig. 1. Homeostatic feedback loop of auditory cortex. Projection neurons (pyramids) and GABAergic interneurons constitute the homeostatic feedback loop of auditory cortex. The activity of pyramidal neurons is controlled by GABAergic neurons through GABA receptors (GABARs) located on presynaptic and postsynaptic membranes.

2011). For sensory processing, inhibition makes significant contributions to the reliability of signal transformation, signal-to-noise ratio (SNR), receptive field properties, etc (Cardin et al., 2009; Zhu et al., 2015). A proper balance between excitability and inhibition is critical for central information processing. When the pyramidal neuron is overstimulated and the activity is increased higher than the working range, GABA inhibition is strengthened, which brings the activity of the pyramidal neuron back to its operating range (Hartmann et al., 2008). When the activity of the pyramidal neuron is lower than the working range, the inhibitory effect of GABA is weakened, which makes the activity of the pyramidal neuron return to normal working range (Turrigiano et al., 1998; Kilman et al., 2002).

4.2. Pathological remodeling of central firing rate homeostasis in subjective tinnitus

GABA mediated central firing rate homeostasis plays an important role in the development of tinnitus (Yang et al., 2011; Yang and Bao, 2013; Teichert et al., 2017). As reported, GABA synthase (GAD65) gene knockout could induce tinnitus in normal hearing mice (Miyakawa et al., 2019). GABA enhancers in A1 could eliminate tinnitus in hearing impaired rats (Yang et al., 2011). These results suggest that like other sensory systems, GABAergic negative feedback regulation (NFR) responsible for the regulation of pyramidal activity also exists in the auditory system. These results also suggest that loss of cortical GABA inhibition may be an important cause of tinnitus.

When the cortical input was significantly reduced, the activity of AC pyramidal neurons was significantly decreased, and the activity of GABAergic interneurons could not reach the threshold to play an inhibitory role (Qiu et al., 2000; Yang et al., 2011; Miyakawa et al., 2019). After losing the inhibition of GABAergic interneurons, pyramidal neurons improved their activity by aberrantly increasing their own discharges (Miyakawa et al., 2019). The abnormal enhancement of pyramidal neurons spontaneous discharges is the result of the pathological remodeling of central discharge rate homeostasis. It is an altered excitatory-inhibitory balance in neuronal networks to compensate for the loss of pyramidal activity from significant decrease in cortical input. When transmitted to the cognitive center, this aberrantly enhanced spontaneous discharge is perceived as tinnitus.

4.3. Gain adjustment mode in subjective tinnitus

Tinnitus may be caused by significantly decreased auditory input at a certain frequency, which leads to excessively increased spontaneous discharge in cortical pyramidal cells (Fig. 2). The central firing rate homeostatic mechanism can change the gain factor (g) of cortical pyramidal neurons to regulate their discharge rates. According to a tinnitus calculation model (Schaette and Kempter, 2006), when the activity of pyramidal neurons is within the normal working range, g value is equal to 1 ($g = 1$). When their activity is higher than the working range, GABA inhibition increases and g value decreases ($g < 1$), restoring the activity to the working range. When the activity of pyramidal neurons is lower than the normal working range, g value becomes greater than 1 ($g > 1$) as the activity of GABAergic neurons decreases. In a biological system, physiological constraints may impose an upper limit of the gain factor (g_{max}) (Schaette and Kempter, 2006). When the g value reaches its physiological g_{max}, the activity of pyramid cells cannot be restored and an excessive gain ($g > g_{max}$) follows, which can result in pathological hyperactivity of pyramid cells, achieved by their increased spontaneous discharge at the expense of signal-to-noise ratio (S/N) (Schaette and Kempter, 2006), and leads to tinnitus.

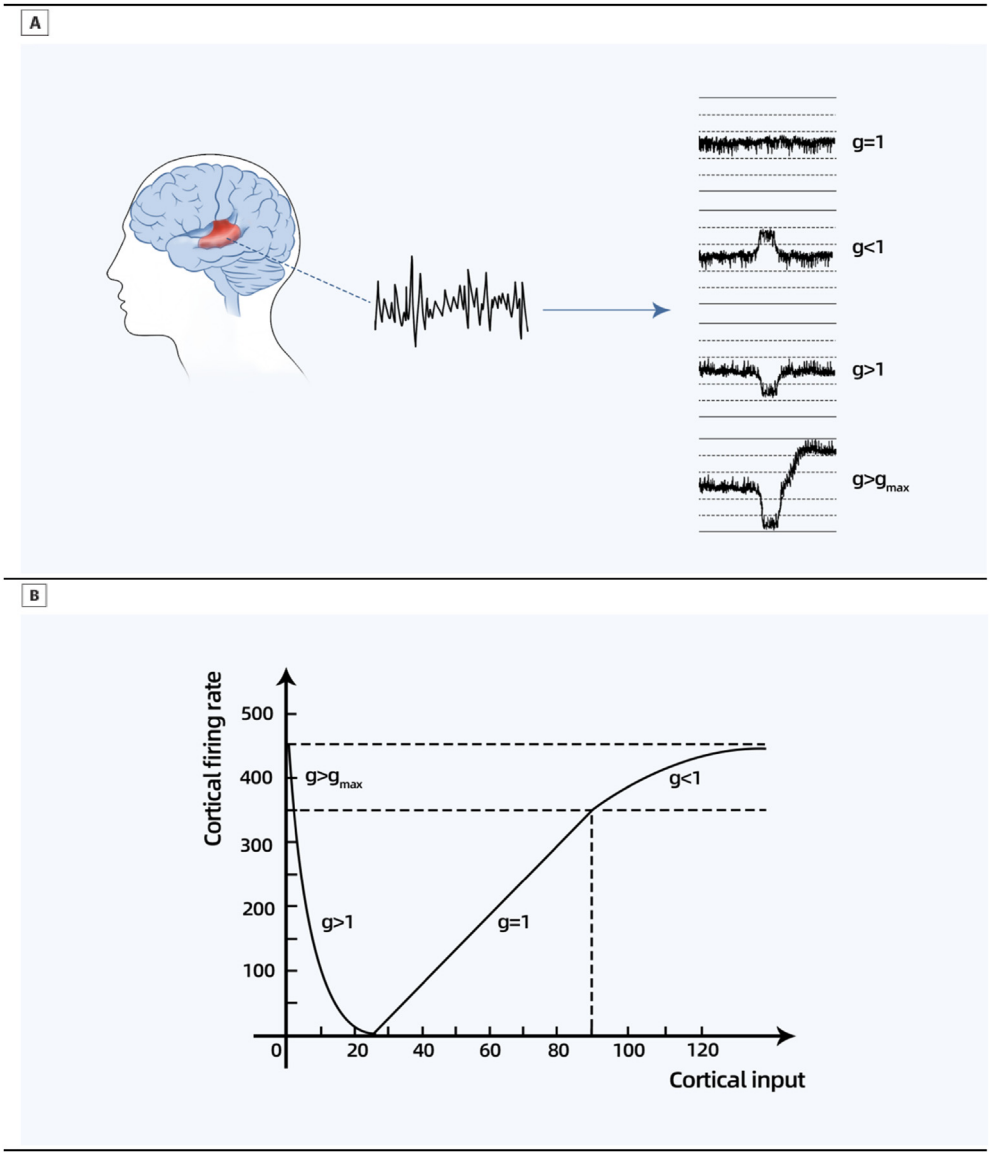

Fig. 2. Central firing rate homeostasis and subjective tinnitus. A. Homeostatic plasticity of auditory cortex under different cortical inputs. When the cortical input decreased significantly, the activity of cortical projection neurons increased abnormally due to the disinhibition of GABAergic interneurons. B. Changes of the gain of cortical pyramidal neurons under different cortical inputs. According to the tinnitus calculation model[62], the gain factor (g) can be equal to 1 ($g = 1$) when the activity of pyramidal neurons is within the normal working range. When the activity of the pyramidal neuron is above or below the normal working range, the g value is reduced ($g < 1$) or increased ($g > 1$) seperately, which brings the activity of the pyramidal neuron back to its operating range. If the g value of the pyramid reaches the physiological maximum (g_{max}) and the activity of the pyramid still can not return to the normal working range, an pathologically increased gain ($g > g_{max}$) will happen, which is perceived as tinnitus by the cognitive canter. g, gain factor; g_{max}, maximal physiological gain.

5. Treatment

Although there are a number of treatment options for subjective tinnitus, including hearing aids (HA) (Del Bo and Ambrosetti, 2007), cochlear implants (CI) (Ramos Macias et al., 2015), drug therapies (Richardson et al., 2012), transcranial magnetic stimulation (TMS) (Piccirillo, 2016) and electrode implantation AC (ACEI) (De Ridder et al., 2007), none of them completely eliminates tinnitus. According to the analysis above, two strategies should be considered in the management of subjective tinnitus: restoring cortical input and eliminating pathological hyperactivity. Cortical GABA inhibition may play a key role in the pathogenesis of subjective tinnitus (Miyakawa et al., 2019; Yang et al., 2011). Selective cortical GABAergic interneurons agonists may be a potential way to eradicate subjective tinnitus in the future (Shulman, 1995; Shulman et al., 2002; Hamilton et al., 2013; Deng et al., 2020).

6. Summary and prospect

This article reviews the etiology, location and pathogenesis of subjective tinnitus. Subjective tinnitus is caused by decreased cortical input due to damage of the peripheral auditory pathway or central nervous system. AC plays a key role in the pathogenesis of subjective tinnitus and may be the place where it originates. The limbic system is related to emotional changes in tinnitus patients. Based on the latest tinnitus research, we propose a hypothesis of pathological remodeling of central firing rate homeostasis in subjective tinnitus, i.e. significantly decreased auditory input leads to GABAergic interneurons disinhibition and pathological increase of spontaneous discharge in AC projection neurons, which may be the

final common pathway to generation of subjective tinnitus (Table 1). Based on this hypothesis, drugs that selectively enhance cortical GABA inhibition may be important targets for future treatment of subjective tinnitus. Although this is a theoretically reasonable hypothesis (Turrigiano and Nelson, 2004; Schaette et al., 2006; Norena, 2011; Yang et al., 2011; Yang and Bao, 2013; Teichert et al., 2017) with support by some studies from different aspects (Miyakawa et al., 2019; Yang et al., 2011), more systematic and detailed studies are needed for further verification.

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Declaration of competing interest

This manuscript describes the original work, which has not been considered by other magazines. The author states that there is no conflict of interest in the publication of this paper.

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