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NMDA Receptors: Next therapeutic targets for Tinnitus?

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ABSTRACT

Tinnitus, a common otological symptom, lacks clinically approved pharmacological treatments, highlighting an urgent unmet need. This review explores the potential role of NMDARs, key glutamate receptors in the auditory system, in tinnitus pathophysiology, including excitotoxicity, synaptic plasticity, and neuropathic pain. Alterations in NMDAR variants with different subunit compositions during development have also been implicated in the onset of tinnitus. Clinical trials of NMDAR antagonists, such as acamprosate, caroverine, neramexane, and AM-101, have shown promising results, though none are yet approved. These findings highlight the need for further research on NMDARs to advance the development of next-generation targeted pharmacological therapies for tinnitus.

1. Introduction

Tinnitus is the perception of sounds in the ears or head in the absence of an external source or an outside stimulation. It is the most common symptom in otology, and the prevalence of tinnitus increases with age, reaching a peak at the seventh decade of life [1,2]. The incidence has increased among younger group over the past decade [3,4]. Due to the complex etiology and unclear pathophysiological mechanisms of tinnitus, it remains an urgent but unresolved clinical problem [5].

Currently, it is widely believed that the pathophysiological mechanisms of tinnitus are based on abnormal activity and central nervous system reorganization of the auditory pathway, involving multiple complex neural pathways, including auditory and non-auditory pathways. Acute tinnitus (less than 3 months) and chronic tinnitus (greater than or equal to 3 months) may have different neurological mechanisms. In the acute stage of tinnitus, it is usually caused by peripheral damage, such as damage to cochlear hair cells (HCs) by noise or drugs. Abnormal HC output leads to abnormal activity at the synapses of inner hair cells (IHCs) and spiral ganglion neurons (SGNs), resulting in increased spontaneous discharge of peripheral auditory nerve fibers. The abnormal discharge behavior of the peripheral auditory pathway ultimately affects the central auditory neural circuits, leading to a rapid increase in neuronal activity in the hypothalamus and short-term neuroplasticity adjustments in the auditory cortex to adapt to the sudden changes in auditory input [6].

In the chronic stage of tinnitus, the pathogenesis becomes more complex. The neural networks in the auditory cortex undergo reorganization, leading to persistent increases in excitability. Abnormal signal transmission between the thalamus and cortex may amplify and sustain the tinnitus signal. Furthermore, a reduction in inhibitory neurotransmission, particularly a decrease in GABAergic inhibition, leads to enhanced excitability of the auditory pathway. In the chronic stage, multiple neural networks are involved, including emotional and attentional networks [7]. The limbic system, such as the amygdala, and the prefrontal cortex may influence the emotional response to and attentional allocation towards tinnitus. The default mode network may also play a role in the persistent perception of tinnitus, affecting an individual's subjective experience. Long-term tinnitus is often accompanied by emotional and cognitive changes, such as anxiety and depression, which in turn may exacerbate tinnitus. Therefore, acute tinnitus primarily involves peripheral damage and peripheral-central nervous system changes, while chronic tinnitus involves long-term reorganization of the central nervous system and complex interactions among multiple networks, with emotional and cognitive factors also playing important roles [8].

Based on the above pathological mechanisms, theoretical interventions for tinnitus can modulate abnormal neural activity, reduce excitability of the auditory pathway, promote reorganization of the auditory system to reduce tinnitus perception, and improve cognitive and emotional responses to tinnitus. Current commonly used treatment methods include sound therapy, cognitive-behavioral therapy (CBT), pharmacotherapy, and physical therapy [9]. Sound therapy can mask

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tinnitus using white noise or natural sounds to help patients reduce tinnitus perception. It can also promote reorganization of the auditory system through specific sound training to reduce tinnitus perception [10]. CBT can help patients change their cognitive and emotional responses to tinnitus, reducing the stress caused by tinnitus. Physical therapy often includes transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), aimed at altering the excitability of auditory neurons [11]. Pharmacotherapy aims to modulate abnormal neural activity, for example, benzodiazepines enhance GABAergic inhibition, and glutamate receptor antagonists can reduce glutamatergic excitatory activity. Currently, there is no consensus internationally on these therapies, and pharmacotherapy for tinnitus is not recognized or considered to play only an adjunctive role in most countries' guidelines [12,13]. However, pharmacotherapy has the advantages of intuitive efficacy and high patient compliance, and this field has been a research hotspot in tinnitus treatment. With the increasing understanding of the pathophysiological mechanisms of tinnitus, we believe that drugs have potential efficacy for tinnitus.

Glutamate, as the most common excitatory neurotransmitter in the auditory pathway, is also one of the ideal intervention targets for tinnitus treatment. Glutamate receptors in the nervous system are mainly divided into two categories: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs) [14]. *N*-methyl-D-aspartate receptors (NMDARs), a type of iGluRs, are the most widely distributed glutamate receptors in the auditory system, extensively present in multiple sites of the auditory system, including the cochlea, inferior colliculus, and auditory cortex. NMDARs play an important role in the process of auditory generation and are involved in synaptic plasticity, such as long-term potentiation (LTP) [15]. In the process of tinnitus onset, NMDARs are pathologically over-activated [16]. Therefore, in recent years, many clinical studies have explored the therapeutic effects of NMDAR antagonists on tinnitus, including memantine, acamprosate, caroverine, neramexane, etc. Although the evidence from research results is mixed and insufficient to prove the general effectiveness of NMDAR antagonists for tinnitus, they still provide a sufficient research foundation for the study of NMDAR antagonists in tinnitus treatment. This review will discuss the relationship between NMDAR and the occurrence of tinnitus, the current state of research on NMDAR antagonists for tinnitus treatment, and the difficulties and possible future directions of NMDAR antagonist drug treatment.

2. Glutamate receptors in the auditory system

Glutamate is the most common excitatory neurotransmitter in the auditory system, and glutamate receptors are widely distributed across auditory neurons at various levels. Metabotropic glutamate receptors (mGluRs), primarily consisting of eight subtypes (mGluR 1-8), are extensively distributed throughout the different layers of the auditory system, including the cochlea, thalamus, and auditory cortex. These receptors modulate neuronal excitability and synaptic plasticity by influencing intracellular calcium levels and other signaling molecules via G protein-coupled signaling pathways. Ionotropic glutamate receptors (iGluRs) mainly consist of NMDARs, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPARs), and kainate receptors (KARs) [14]. AMPARs are widely expressed throughout the auditory system, including in spiral ganglion neurons (SGNs), the cochlear nucleus, the superior olivary complex (SOC), the inferior colliculus (IC), and the auditory cortex. These receptors are the primary mediators of fast excitatory synaptic transmission in the central nervous system [17]. Characterized by high Na^{+} permeability and low Ca^{2+} permeability, AMPARs facilitate rapid postsynaptic depolarization, producing millisecond-scale synaptic currents essential for the precise encoding and relay of temporal auditory information [18]. The GluA2 subunit of AMPARs plays a critical role in this process by conferring rapid desensitization properties, allowing neurons to respond effectively to high-frequency auditory input. Additionally, the activity-dependent insertion or removal of AMPARs from the postsynaptic membrane serves as a key mechanism underlying synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD) at auditory synapses [19]. In contrast, KARs exhibit a more restricted distribution within the auditory system, with limited expression reported in SGNs, the cochlear nucleus, the IC, and the auditory cortex. Presynaptically, KARs are involved in fine-tuning synaptic transmission via a negative feedback mechanism that modulates glutamate release. Their slow gating kinetics suggest a functional role in balancing synaptic strength and supporting the temporal integration of auditory signals [20]. Furthermore, KARs may influence auditory plasticity indirectly by modulating AMPAR function [21,22]. Despite these insights, current understanding of KARs in the auditory system remains limited. The specific mechanisms by which KARs contribute to auditory processing and plasticity are still poorly understood, highlighting the need for further investigation.

NMDARs are the most widely distributed glutamate receptors in the auditory system, extensively present in multiple auditory regions including the cochlea, thalamus, and auditory cortex. Consequently, NMDARs have been the subject of relatively more research in the fields of auditory medicine and tinnitus. Unlike neurotransmitter receptors in general, NMDARs have some unique properties. Firstly, NMDARs are ligand-gated and voltage-dependent cation channels which can be blocked by extracellular Mg^{2+} in a voltage-dependent manner. It requires diminishing Mg^{2+}-block by independent depolarization of membrane potential and the presence of corresponding ligands to open the ion channels. Secondly, NMDARs are regulated by double ligand gating since it has allosteric modulatory sites [23]. The agonist—glutamate and the co-agonist—glycine or D-serine must bind to their respective binding sites on the receptor to maintain ion channel gating, while the single agonist fails to open the channel [24]. Thirdly, NMDARs are permeable to Na^{+}, K^{+}, and Ca^{2+}, and in particular its high permeability to Ca^{2+} is associated with the development of excitotoxicity and neural plasticity which are important neurological bases of tinnitus [25].

Although both of NMDARs and APMARs are iGluRs on the postsynaptic membrane, they show different gating kinetics. The fast and temporally precise encoding of sound is dependent on APMARs which mediate fast excitatory synaptic transmission lasting less than 1 ms [26]. However, NMDARs are responsible for encoding slow- and long-lasting sound and the process of activation and deactivation usually lasts tens of milliseconds, some even reaching thousands of milliseconds.

NMDARs are located not only in the synapses between hair cells (IHC) and spiral ganglion neurons (SGNs) in the cochlea but in the central auditory nucleus in the brainstem. Several recent studies have reported the distribution of NMDARs in the cochlear nucleus including dorsal cochlear nucleus (DCN) and ventral cochlear nucleus (VCN) [27,28]. For example, DCN fusiform neurons and cartwheel interneurons expressed NMDARs mainly at their apical dendrites, while the basal dendrites of fusiform neurons seldom expressed NMDARs [21].

NMDARs consist of three types of subunits including GluN1, GluN2A, B, C, D, and GluN3A, B. Since GluN3 is a rare subunit, the majority of NMDARs in the auditory pathway are heterotetramers composed of two GluN1 and two GluN2. GluN1 is considered to act as a mandatory subunit to express all pharmacological activity and GluN2 is a regulatory subunit to modulate the activity of GluN1. NMDARs where the GluN2B subunit predominates show slow gating kinetics (lasting hundreds of milliseconds) while those where the GluN2A subunit predominates show fast gating kinetics (lasting tens of milliseconds). Besides, the composition changes with the development of the synapses [29]. In early developmental auditory synapses, NMDARs usually contain more the GluN2B subunit. When auditory synapses mature, GluN2B is downregulated and GluN2A is upregulated [30]. However, it is opposite in IHC-SGN synapses. The synapses during early development show a transient expression of GluN1 and GluN2A. With maturation, GluN1 and

GluN2A are obviously downregulated or even completely eliminated while GluN2B, C, and D are upregulated [31]. The opposite expression of subunits in IHC-SGN synapses is possibly related with regulation the expression of AMPARs [21].

Recent research advances suggest that NMDARs are not only localized within synapses but can also exist in extra-synaptic regions, distant from direct synaptic contact points. The composition and function of NMDARs vary depending on their cellular localization. Synaptic NMDARs (sNMDARs), situated at the postsynaptic membrane of synaptic sites, are typically composed of two GluN1 and two GluN2 subunits [32]. Upon binding with glutamate, sNMDARs open ion channels, promoting calcium influx and activating various signaling pathways that support neuronal excitability and information processing. This is the classic mode of action for NMDARs, primarily involved in synaptic transmission and plasticity. Extra-synaptic NMDARs (eNMDARs) are tetramers composed of either two GluN1 and two GluN2 subunits or two GluN1, one GluN2, and one GluN3 subunit. By activating different signaling pathways, eNMDARs may influence cell survival. The activation of eNMDARs is associated with neuronal apoptosis, as it can upregulate the transcription of pro-apoptotic genes, including caspase-3 and FOXO, while downregulating the transcription of pro-survival genes such as CREB, MAPK, and ERK1/2[33]. This suggests that eNMDARs may play a role in neurodegenerative changes. Furthermore, research indicated that eNMDARs mediated chronic excitotoxicity and contributed to the pathogenesis of Alzheimer's disease. In contrast to the phasic, strong activation of sNMDARs, eNMDARs exhibit tonic, persistent, weak activation [34]. Currently, research on eNMDARs is primarily focused on the central nervous system and neurodegenerative disorders, with limited reports in the peripheral auditory system and auditory medicine. However, extra-synaptic NMDARs may provide a new research direction for investigating the pathological mechanisms of chronic tinnitus.

3. NMDA receptors and their roles in tinnitus

3.1. Overactivation of NMDARs in salicylate-induced acute tinnitus

Animals receiving administration of high doses of salicylates develop tinnitus and hearing loss, which are considered as a commonly used animal models of tinnitus due to the stability and high efficiency [35]. It is reported that the increased expression levels of NMDAR subunit GluN2B were observed in salicylate-induced acute tinnitus models [36]. Further investigations found that salicylates increased NMDAR sensitivity and overactivated NMDARs which contributed to occurrence of acute tinnitus [31]. Besides, tinnitus was significantly relieved after administration of NMDAR antagonists in salicylate-induced tinnitus models.

Salicylates are a classical type of non-steroidal anti-inflammatory drugs (NSAIDs) that function as the inhibitor of Cyclooxygenase-2 (cox2). Then, the levels of intracellular arachidonic acid (AA) are increased in a cellular environment with the attenuating activity of cox2 which can facilitate conversion of AA to prostaglandin (PG) in vivo [37]. Excessive AA improves NMDAR sensitivity to glutamate as well as promotes generation of reactive oxygen species (ROS) and development of inflammation, damaging inner hair cells and other auditory neurons. Based on the above, NMDARs are finally overactivated, which evokes excessive intracellular Ca^{2+} influx and excitotoxicity in the auditory neurons, thereby resulting in the development of tinnitus and hearing loss [38].

Besides, NMDAR antagonists have significant therapeutic effects on salicylate-induced acute tinnitus [39]. For example, a recent study demonstrated that the expression levels of GluN2B and related genes TNFα, intracellular ROS levels, and induced expression of cleaved caspase-3 were measured to rise after administration of salicylates in the control group without intervention of NMDAR antagonists [40]. In the experimental group with the pretreatment of valproic acid (VPA), a regulator of NMDARs, the above salicylate-induced tinnitus-related changes were attenuated compared to the control group. These evidences support that VPA has beneficial effects in a salicylate-induced temporary hearing loss and tinnitus model.

3.2. NMDAR feed-forward mechanism drives SGN excitotoxicity in chronic injury

SGN excitotoxicity, acknowledged as an important neurological factor of tinnitus development, occurs when hyperactivation of iGluRs on the postsynaptic membrane by prolonged exposure to glutamate triggers excessive influx of ions and water into SGNs [41]. As the trial results demonstrated, intracellular Ca^{2+}-overload is considered as the key point in the formation of SGN excitotoxicity, which activates proteases, phospholipases, NO synthases, and endonucleases, resulting in cytoskeleton breakdown, free radical production, and DNA breakdown (Fig. 1). These activities eventually cause SGN injury or even death [42]. Substantial SGN deaths not only lead to hearing impairment but can possibly induce frequency-specific spontaneous firing in cochlear nucleus for the compensation of neural input loss from the cochlea, which provides neurological basic for tinnitus development [35]. Besides, the recent study reported that the activation of NMDAR feed-forward mechanism under chronic insult could increase glutamate release and activate NMDARs at a high level, thereby inducing SGN excitotoxicity and tinnitus [43].

NMDAR feed-forward mechanism is that NMDARs are upregulated to protect SGNs when the inner ear is stimulated by acute injury but substantial damage to auditory neurons has not yet happened, because NMDARs can regulate AMPAR expression and assist in the restoration of synaptic inputs functioning as protective and neurotrophic roles following acute insult [44]. In the experiments by d'Aldin having revealed NMDAR neurotrophic roles, inhibiting NMDARs delayed SGN dendritic regeneration onto IHCs, the formation of synapses, as well as the recovery of cochlear function compared to the control group with normal NMDAR expression [45]. When the inner ear is acutely injured, this feed-forward regulation would be initiated, increasing glutamate emission from IHC synaptic terminals in into synaptic cleft. The elevated levels of glutamate in synaptic cleft activate a growing number of NMDARs to protect SGNs from damage by NMDAR neurotrophic effects. Thus, NMDAR feed-forward regulation can prevent foreseeable impairment to SGNs following acute insult [45](Fig. 2).

NMDAR expression levels were also observed to increase when suffering from long-term chronic injury due to the initiation of the feed-forward mechanism, which, however, was a contributory factor in development of SGN excitotoxicity and further lead to tinnitus. Under a chronic injury, excessive glutamates are released from IHCs in into synaptic cleft and NMDAR expression is upregulated for a long time evoking Ca^{2+}-overload in SGNs. Thus, chronic insult activates the feedforward system over time and NMDARs do not perform its neurotrophic roles as well as expected. Instead, intracellular Ca^{2+}-overload prompts excitotoxicity development. Thus, prolonged and incorrect activation of NMDAR feedforward system by chronic insult helps the formation of SGN excitotoxicity [46].

3.3. NMDAR-mediated long-term plasticity as a trigger for tinnitus

In the experiments of animals with behavioral evidence of tinnitus, the long-term synaptic plasticity is firstly observed in DCN neurons [47]. Maintaining and altering neural plasticity depends on long-term potentiation (LTP) and long-term depression (LTD) of excitatory synaptic responses between neurons. According to some research findings, LTP and LTD of DCN fusiform neurons and cartwheel interneurons are NMDAR-dependent. At NMDAR-expressing apical dendrites of fusiform neurons and cartwheel interneurons, LTP and LTD can be observed, while both of them disappear at the basal dendrites of fusiform neurons where NMDARs are seldom expressed. Besides, LTP and LTD can be significantly diminished after the administration of NMDAR antagonists.

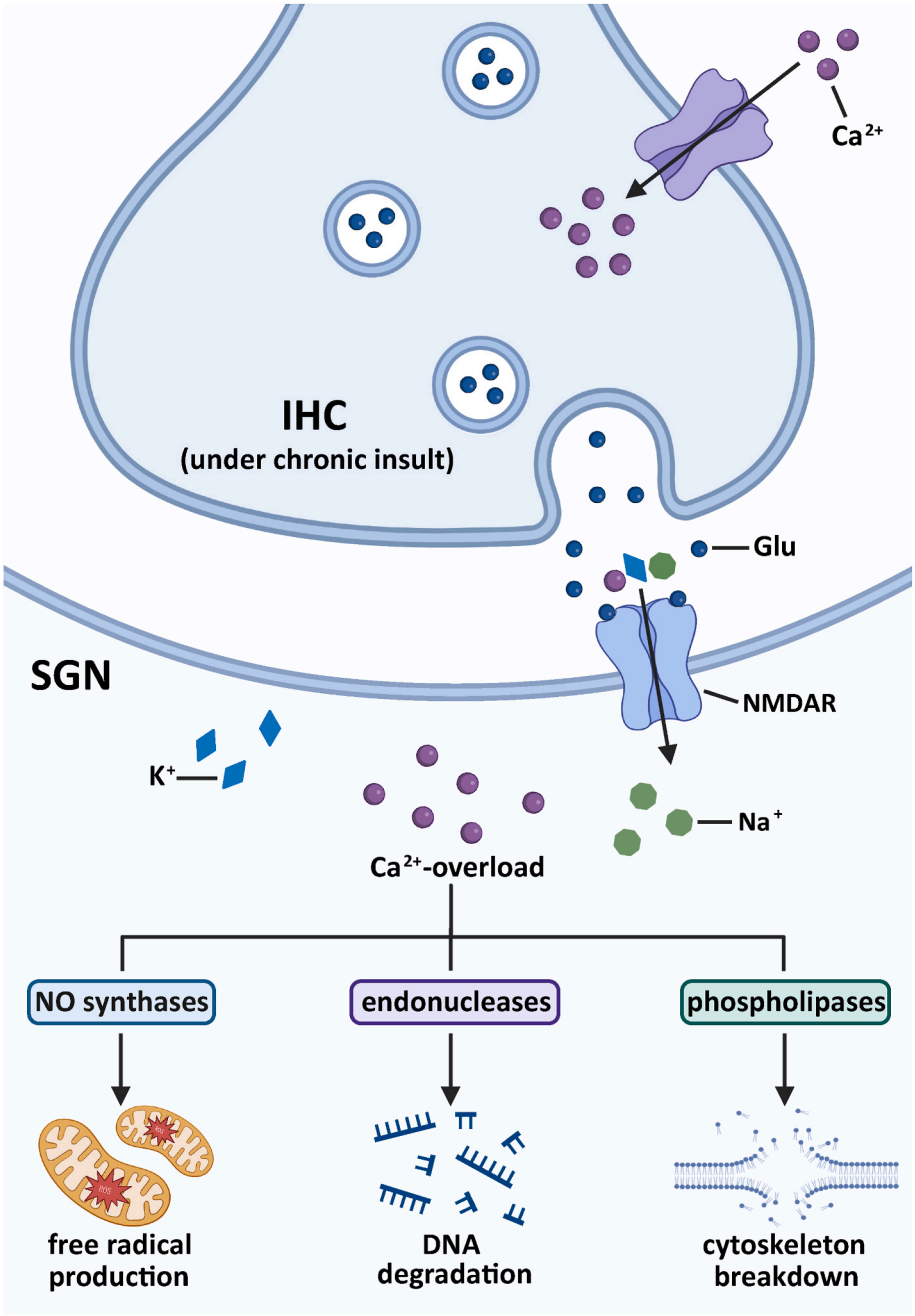

Fig. 1. SGN excitotoxicity is induced by the hyperactivation of NMDARs by prolonged exposure to glutamate triggers excessive Ca^{2+} influx into SGNs [41]. Besides, intracellular Ca^{2+}-overload is of cardinal significance in the formation of SGN excitotoxicity, which activates Ca^{2+} -dependent enzymes including phospholipases, NO synthases, and endonucleases, resulting in cytoskeleton breakdown, free radical production, and DNA breakdown. These activities eventually cause SGN injury or even death, i.e., SGN excitotoxicity [35,42,43].

Similarly, regulation of LTP and LTD by NMDAR also depends on increased intracellular Ca^{2+} concentrations that activate multiple calcium-dependent enzymes in postsynaptic neurons including CaMK, CaN, PKC, PLA2, PLC, NOS and some proteases [48,49]. Then they change synaptic strength and mediate the balance between LTP and LTD. Thus, NMDARs mediate long-term synaptic plasticity in DCN by balancing LTP and LTD [50].

Synaptic plasticity plays a key role in the occurrence of increased spontaneous firing and discordant neural activities in the auditory pathway, so it is considered an important pathophysiological basis for tinnitus development [8,31]. When the cochlea is injured by noise trauma, SGN excitotoxicity, or other harmful factors, auditory nerve fiber input from cochlea to cochlear nucleus is attenuated [51]. To compensate of the input loss, cochlear nucleus alters its long-term plasticity and homeostatic by upregulating NMDARs as well as deregulating some inhibitory neurotransmitter receptors such as GABA receptors [52]. Therefore, altered neural plasticity induces frequency-specific increases in spontaneous firing rates in the neurons of DCNs [53,54]. This increased activity is further transmitted via inferior colliculus to medial geniculate body (MGB) and propagates to primary auditory cortex, leading to increased spontaneous firing rates, increased synchronization, and increased burst firing at different levels of the auditory pathway and eventually resulting in tinnitus [55]. In addition, a related study showed that the neurons in MGB were hyperpolarized due to the propagation of the increased discharge from the cochlear nucleus to the auditory thalamus. Then, the hyperpolarization

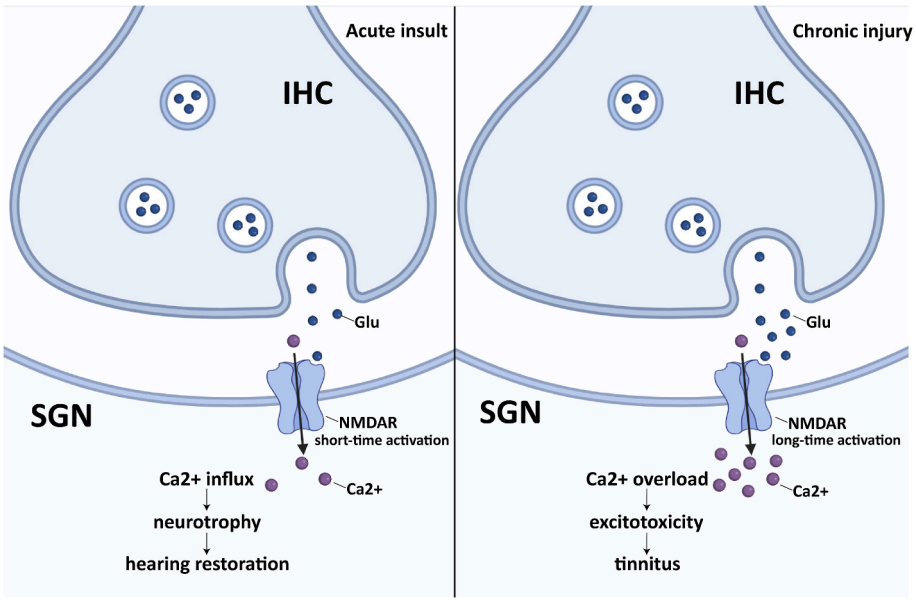

Fig. 2. NMDAR feed-forward mechanism, upon activation by acute and chronic injury, leads to two opposite outcomes respectively [44]. (A) Under acute insult, short-time activation of the feed-forward regulation exerts neurotrophic effects of NMDAR and protects SGNs from damage. (B) However, under chronic injury, the prolonged feed-forward regulation leads to hyperactivation of NMDARs evoking excessive Ca^{2+} influx, which further causes SGN excitotoxicity and contributes to tinnitus development [45].

of the MGB neurons can in turn lead to changes in low-frequency and gamma oscillations in the auditory cortex, which aggravates dysrhythmia in the auditory cortex and contributes to producing the perception of tinnitus in the brain (Fig. 3).

Moreover, the modulation of synaptic plasticity is not exclusively dependent on NMDARs. As research in the central nervous system advances, it is becoming increasingly evident that neural plasticity is regulated by a complex network in which NMDARs serve as a central component, but are influenced by interactions with astrocytes and a variety of neurotransmitters. In the somatosensory cortex and hippocampus, for instance, astrocytes release D-serine—a co-agonist of NMDARs—in a Ca^{2+}-dependent manner, thereby facilitating the activation of postsynaptic NMDARs and contributing to the regulation of LTP and LTD [56,57]. In the auditory system, specifically at the synapses of the MGB and auditory cortex (AC), studies have shown that astrocyte-mediated signaling can influence presynaptic activity. In particular, the release of ATP/adenosine by astrocytes and their interaction with adenosine receptors modulate glutamate release, ultimately affecting the induction of LTP and LTD at MGB–AC synapses [58]. However, the precise involvement of NMDARs in this modulatory pathway has not been fully elucidated. Taken together, these findings suggest the existence of a regulatory network centered around NMDARs, modulated by astrocytes and multiple neurotransmitter systems, which may contribute to the neural plasticity changes underlying tinnitus development. Despite these insights, the specific roles of astrocytes, D-serine, and adenosine in the auditory system—and their implications for tinnitus pathology—remain insufficiently characterized. Additionally, clinical trials targeting these components in the context of tinnitus are currently limited, highlighting an important avenue for future investigation.

3.4. Dynamic alterations in NMDAR variants contribute to tinnitus pathogenesis

NMDARs are heterotetrameric ion channels typically composed of two GluN1 subunits and two additional subunits from either the GluN2 (A–D) or GluN3 (A–B) families. Variations in subunit composition give rise to a wide array of receptor isoforms—over a thousand NMDAR variants have been documented in the NIH ClinVar database. These variants exhibit distinct properties in gating kinetics, synaptic transmission, and neuroplasticity.

Emerging evidence suggests that the onset of tinnitus may be associated with developmental changes in NMDAR subunit composition that influence synaptic plasticity [59]. During auditory system maturation, GluN2B expression is initially high but becomes downregulated over time, while GluN2A expression increases with age [30]. Although the precise functional roles of individual NMDAR subunits in auditory circuits remain incompletely understood, insights from other brain regions offer some guidance. For example, in the somatosensory cortex of mice, spike timing-dependent long-term depression (t-LTD) is prominent between postnatal days 13–21 and declines after the fourth week of development. This form of plasticity is dependent on the activation of GluN2B-containing NMDARs [56]. Similarly, in the hippocampus and primary visual cortex, LTD is more pronounced before the fourth postnatal week and is mediated by GluN2C/D-containing receptors, whereas LTP becomes dominant after the fifth week and involves GluN2A/B subunits [57,58,60]. These findings collectively demonstrate that age-dependent shifts in NMDAR subunit composition significantly influence the direction and magnitude of synaptic plasticity. Extrapolating from these data, we hypothesize that during auditory system development, a transition from GluN2B-dominant to GluN2A-dominant NMDARs may disrupt the balance between LTD and LTP in auditory pathways. Such an imbalance in neuroplasticity could underlie the pathophysiological mechanisms that trigger tinnitus. This hypothesis aligns with epidemiological data indicating that the prevalence of tinnitus increases with age, reaching a peak around 70 years [1,2]. Nevertheless, the specific contributions of individual NMDAR variants during auditory system development remain underexplored. Further research is needed to delineate how subunit-specific changes influence auditory neuroplasticity and susceptibility to tinnitus.

In summary, developmental alterations in NMDAR subunit composition may play a critical role in shaping synaptic plasticity within the auditory system, thereby contributing to age-related tinnitus pathogenesis. Given that the functional role of NMDARs evolves with subunit transitions and maturation, future studies should consider both subunit-specific pharmacological targeting and therapeutic timing to optimize

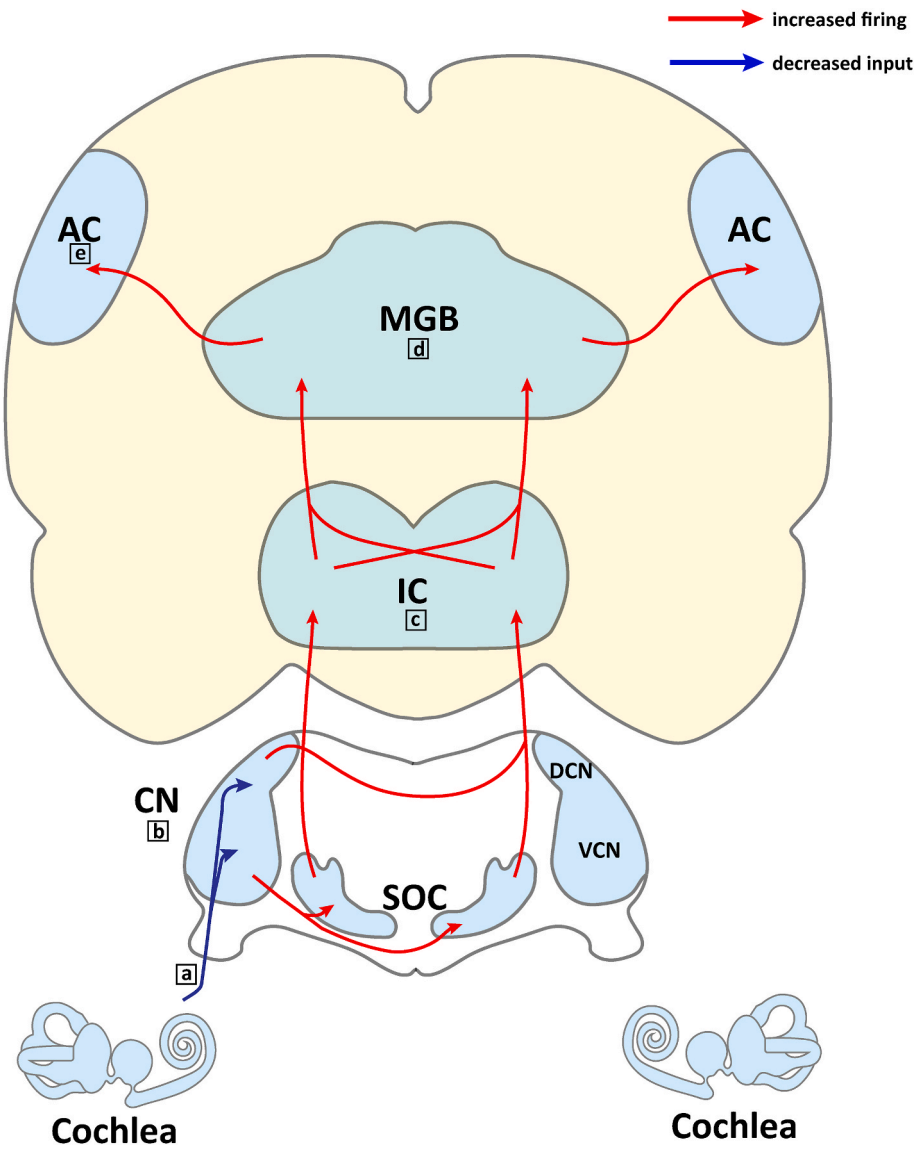

Fig. 3. Synaptic plasticity evokes spontaneous firing originating at the cochlea nucleus (CN) for compensation of the input loss from cochlea and propagate this increased activity to superior auditory pathway. (a) When the cochlea is injured by some harmful factors, auditory nerve fiber input from cochlea to cochlear nucleus is attenuated [50]. (b) Frequency-specific spontaneous firing rates occur in CN and is transmitted to the inferior colliculus (IC) via the superior olivary complex (SOC) or not [51]. (c) In IC, it induces increased bursting and cross-fiber synchrony. (d) In the medial geniculate body (MGB), increased synchronization and burst firing as well as hyperpolarization of the neurons are discovered. (e) The propagation of the increased discharge triggers dysrhythmia in the auditory cortex (AC) and produces the perception of tinnitus in the brain [58].

precision treatment strategies for tinnitus.

3.5. NMDARs link chronic orofacial pain to increased glutamatergic input from somatosensory to auditory pathways

Recently, it is clinically common for some tinnitus patients to experience relief from tinnitus-related intensity and frequency by stimulating or moving their face and neck [61]. This phenomenon suggests that the interaction between auditory and somatosensory structures plays a crucial role in the development of tinnitus. Moreover, this type of tinnitus, often referred to as "somatosensory tinnitus" or "somatic tinnitus", is prevalent among tinnitus populations, affecting up to two-thirds of patients with tinnitus [62].

Fusiform cells in the DCN are considered as the ideal place for auditory-somatosensory integration, where projections from auditory nerve, trigeminal and dorsal column ganglia, and brain stem nuclei converge [8]. This multisensory integration in DCN fusiform cells depends on mechanisms of maladaptive auditory-somatosensory plasticity, which shows stimulus timing dependent [63]. After decreased auditory nerve input to the cochlea nuclei induced by cochlear damage, non-auditory glutamatergic innervation increases and glutamatergic inputs from somatosensory pathway to DCN are upregulated, leading to tinnitus-related changes in DCN including increased LTP in fusiform cells. Then, the significant alterations in somatosensory-auditory integration in the cochlea nuclei are further transmitted to the auditory cortex, resulting in the development of tinnitus perception [64].

NMDARs can serve as a potential therapeutic target for "somatosensory tinnitus". On the one hand, blocking NMDARs may inhibit an increase in glutamatergic neurotransmission from somatosensory structure following loss of auditory input. On the other hand, NMDAR-mediate chronic orofacial neuropathic pain, acting as a significant component of somatosensory stimulation in the trigeminal nerve, can possibly aggravated pathologically increased neural input from somatosensory pathway to cochlea nuclei. According to some animal

experiments, NMDAR-mediate long-term potentiation (LTP) in the spine and the anterior cingulate cortex (ACC) is hypothesized to underlie chronic pain [65,66]. The pain-related behavioral and morphological alterations can be prevented by blocking NMDARs [67]. Besides, recent research [68] reported that GluN2A and GluN2B subunits mediated peripheral and central sensitization triggering orofacial neuropathic pain. The inferior alveolar nerve transection (IANX) induces ectopic allodynia behavior in mice via promoting the production of peripheral and central sensitization-related molecules such as IL-1β, TNF-α, and so on. Conditional deletion of GluN2A and GluN2B can prevent part of IANX-induced molecular alterations, thereby reversing orofacial ectopic allodynia after IANX. Thus, blocking NMDARs diminishes the neurological inputs of chronic pain from trigeminal ganglia to DCN.

4. Clinical trials of NMDA receptor antagonists for tinnitus

At present, numerous kinds of NMDAR antagonists, including nitrous oxide, memantine, acamprosate, and so on, are useful therapeutics as they prevent the pathological activation of NMDA receptors while not impairing their physiological activity [69]. Unlike potent NMDAR channel blockers producing phencyclidine-like psychotropic symptoms and thereby leading to numerous side effects, the majority of moderate-affinity NMDAR antagonists, such as memantine and neramexane, show great safety and tolerability by tinnitus patients in clinical studies [70]. There are a number of clinical trials having investigated the therapeutic efficacy of various NMDAR antagonists for tinnitus, but strangely, some clinical studies have reached diametrically opposite conclusions, which may be due to the fact that tinnitus is multifactorial [71]. Thus, drugs with the same target can possibly yield opposite results in treating tinnitus patients with diverse etiology and pathogenesis. Then, we collected some clinical trials of NMDAR antagonists for tinnitus and their results (Table 1).

Furthermore, in the clinical trial results of NMDAR antagonists for tinnitus treatment, we labeled and categorized patients with acute and chronic tinnitus. As previously mentioned, the distinct pathophysiological mechanisms and clinical manifestations of acute and chronic tinnitus necessitate different treatment principles [12,13]. In clinical practice, the primary focus of acute tinnitus management is on treating the underlying cause, aiming for early intervention to eliminate the causative factors and prevent the progression from the acute to the chronic stage. In contrast, the management of chronic tinnitus places greater emphasis on long-term tinnitus management. Chronic tinnitus often leads to remodeling of the auditory central nervous system, altering the brain's processing of tinnitus sounds. This remodeling may involve multiple aspects, including neuronal rewiring, changes in synaptic plasticity, and reorganization of neural networks, consequently affecting the transmission and integration of auditory information. Patients with chronic tinnitus frequently present with concomitant symptoms such as anxiety, depression, insomnia, and metabolic disorders. Treatment for chronic tinnitus primarily focuses on alleviating or eliminating these accompanying symptoms [10]. Therefore, the therapeutic objectives for chronic tinnitus are long-term management, reduction of symptom severity and associated complications, and improvement of the patient's quality of life. Consequently, we have independently analyzed and evaluated the efficacy of various NMDAR antagonists for acute and chronic tinnitus. This approach aims to provide a more comprehensive assessment of their therapeutic effects on tinnitus, considering the specific characteristics of each subtype.

Nitrous oxide, primarily as a non-competitive antagonist at NMDARs, binds near the phencyclidine (PCP) binding site within the ion channel, thereby inhibiting calcium influx. It was evaluated in a randomized, placebo-controlled crossover trial for its therapeutic effect for chronic, subjective, idiopathic tinnitus [72]. The trial respectively measured the mean decline in TFI after intervention in the experimental group (decreased by 2.5) and the control group (decreased by 1.8). The difference in TFI decline between the placebo arm and the nitrous oxide arm was −1.1 points (within 95 %CI, −5.6 to 3.4 points) and failed to demonstrate clinical meaning and statistical significance. The result did not prove the effectiveness of nitrous oxide in the treatment of chronic tinnitus.

Caroverine primarily acts as a non-competitive antagonist to block NMDARs. It likely binds to the ion channel of the receptor, thereby inhibiting the influx of calcium and sodium ions. This mechanism helps to reduce excitatory neurotransmission and may be useful in alleviating tinnitus and other neurological symptoms. It was tested in a placebo-controlled blind study [73]. There were 19 responders out of 30 caroverine-treated patients (63.3 %) showing a reduction in both subjective rating and psychoacoustic measurement (tinnitus matching). In the placebo group none of the 30 patients showed a statistically significant response.

Acamprosate has been shown to modulate the activity of NMDARs. However, the precise binding site and mechanism of action of

Table 1
Clinical trials of NMDAR antagonists for tinnitus.

Drugs	Reference	Subjects	Tinnitus type	Dosage	Administration route	Results
Nitrous oxide	Hong H.Y et al. [72]	40	Chronic tinnitus	NA	Inhalation	No significant difference in TFI between the placebo and nitrous oxide
Caroverine	Denk D.M et al. [73]	60	Chronic tinnitus (58 subjects) and acute tinnitus (2 subjects)	An infusion of maximum 160 mg	Intravenous infusion	Significant tinnitus reduction over placebo
Acamprosate	Azevedo A.A et al. [74]	50	Chronic tinnitus	333 mg/d for 3 months	Oral administration	Significant improvement in VAS over placebo
Acamprosate	Farhadi M et al. [76]	20	Chronic tinnitus	333 mg/d for 1 month	Oral administration	Significant subjective relief and electrophysiological improvement over placebo
Acamprosate	Sharma D.K et al. [77]	40	Chronic tinnitus	333 mg/d for 6 weeks	Oral administration	Significant improvement in the tinnitus score over placebo
Memantine	FigueiredoR.R et al. [80]	60	Chronic tinnitus	20 mg/d for 3 months	Oral administration	No significant improvement in THI score over placebo
Neramexane	Suckfüll M et al. [81]	431	Chronic tinnitus	25/50/75 mg/d for 4 months	Oral administration	Significant improvement in THI-12, tinnitus annoyance and impact on life at the medium and high dose
AM-101	Muehlmeier G et al. [83]	24	Acute tinnitus	A 250-μl dose of 0.03/0.09/0.27/0.81 mg/ml	intratympanic injection	Significant improvement in tinnitus loudness, tinnitus handicap, and tinnitus distress at the high dose
AM-101	Staecker H et al. [84]	85	Acute tinnitus	single or triple doses of 0.81 mg/mL	intratympanic injection	Significant improvement in tinnitus loudness, annoyance, sleep difficulties and the THQ over placebo, but no significant difference between the different doses
AM-101	Staecker H et al. [85]	343	Acute tinnitus	3 doses of 0.87 mg/mL	intratympanic injection	Safety and well tolerability of repeated intratympanic administration as compared to placebo

acamprosate on NMDARs remain a subject of ongoing research. Acamprosate acts as a weak antagonist of NMDARs, potentially binding to a site distinct from the glutamate and glycine binding sites. It has been proposed that acamprosate may interact with the polyamine modulatory site on the NMDAR complex. Polyamines, such as spermine and spermidine, are endogenous modulators that enhance NMDAR function by increasing the affinity of the receptor for glutamate and glycine. By binding to the polyamine site, acamprosate may reduce the positive modulatory effects of polyamines, thereby attenuating NMDAR-mediated excitatory neurotransmission. Acamprosate showed effectiveness for tinnitus in several randomized controlled trials. A study [74] reported that the number of patients with improvement in VAS in the acamprosate-treated group (86.9 %) was significantly higher ($p = 0.004$; Student's t-test) than in the control group (44.4 %). Besides, no patient in the acamprosate-treated group reported worsening of VAS score [75]. In another study, a significant reduction was observed in THI ($P = 0.006$), TQS ($P = 0\ 007$), and VAS ($P = 0.007$) in the acamprosate-treated group compared to the placebo group. In the meanwhile, there was a significant reduction in Action Potential latency ($P = 0.048$) as well as an increase in the amplitude of distortion product otoacoustic emissions at 4 kHz ($P = 0.048$), which indicated some degree of the electrophysiological improvement in the auditory pathway [76]. Besides, a randomized controlled crossover study by Sharma D. K revealed a statistically significant difference in reducing the tinnitus score between the experimental group (92.5 %) and the control group (12.5 %). And during the trial, the drug was well tolerated without any serious adverse reactions [77].

Memantine is another type of NMDAR antagonist that binds to the phencyclidine (PCP) binding site within the NMDA receptor ion channel. By blocking the ion channel, memantine prevents the influx of Ca^{2+} and Na^{+}, thereby reducing NMDA receptor-mediated excitatory neurotransmission. Furthermore, studies on Alzheimer's disease have revealed that memantine also exhibits a blocking effect on extrasynaptic NMDARs [33]. Memantine has been reported to have a reduction in tinnitus in rat models [78,79]. However, it failed to improve THI scores of tinnitus patients as compared to the placebo in a prospective randomized double-blind crossover 90-day treatment study [80]. On the contrary, the memantine analog neramexane, acting as the blocker of both NMDARs and α9α10 nicotinic cholinergic receptors, was investigated in a 4-month clinical trial [81]. THI-12 scores, tinnitus annoyance and impact on life were significantly decreased after 4-month treatment and 1-month follow-up in the medium- and high-dose (50 mg/d and 75 mg/d) neramexane groups as compared to the placebo while the low-dose (25 mg/d) neramexane group did not differ from placebo. In addition, neramexane showed the great safety and tolerability during treatment of moderate to severe tinnitus.

Aside from chronic tinnitus, there are currently some novel NMDAR antagonists available for the treatment of acute tinnitus [82]. AM-101 is a novel type of NMDAR antagonist developed by Auris Medical, and its specific binding site and mechanism of action have not yet been fully elucidated. It is hypothesized that AM-101 may competitively interact with the glutamate or glycine binding sites on the NMDA receptor, thereby inhibiting receptor activity. By competitively blocking these binding sites, AM-101 can prevent excessive glutamate or glycine from activating the NMDA receptor, thus reducing excessive excitatory neurotransmission. AM-101 demonstrated the effectiveness and safety in the treatment of acute tinnitus by intratympanic injection in some recent double-blind, randomized, placebo-controlled trials. In a phase I/II clinical trial [83], intratympanic injection of the AM-101 significantly improved subjective tinnitus loudness, tinnitus handicap, and psychological health of the participants with acute tinnitus in the high-dose groups (810 μg/ml) as compared to the control group, while the low dose (30, 90, and 270 μg/ml) of AM-101 failed to show a positive treatment effect. Moreover, the study medication and the intratympanic injection procedure were well tolerated by the participants irrespective of the administered dose. Another clinical trial [84] investigated the therapeutic efficacy of single-dose and triple-dose intratympanic injections of 810-μg/ml AM-101. The descriptive statistics showed that both the single-dose group and the triple-dose group got improvement in tinnitus loudness, annoyance, sleep difficulties and the THQ score over placebo. There is no statistically significant difference in the degree of tinnitus improvement between the single-dose treatment and the triple-dose treatment. A double-blind, randomized, placebo-controlled, phase III clinical trial [85] was designed to evaluate the safety and tolerability of repeated intratympanic administration of AM-101. In the study, 343 participants with persistent acute tinnitus after traumatic cochlear injury or otitis media were randomized to receive 3 intratympanic doses of AM-101 or placebo over 3–5 days. As the result reported, repeated intratympanic injections of AM-101 appear to be safe and well tolerated and show some efficacy in certain patient subgroups, but overall, it failed to meet the anticipated primary endpoints.

To conclude, the above clinical trials demonstrated the positive treatment trend and good safety of AM-101 intratympanic injection for acute tinnitus. However, due to the unsatisfactory results of the Phase III trial, further research and analysis are needed regarding its therapeutic effect to determine which acute tinnitus populations might benefit from AM-101 treatment.

5. Discussion

The incidence rate of tinnitus is currently increasing annually and showing a tendency to affect younger individuals. Tinnitus has now become clinically urgent but unmet need [3]. To conquer the dilemma of tinnitus, we believe that the best option is to make breakthroughs in the field of medication therapy such as NMDAR antagonists. However, the role of NMDAR in the development of tinnitus is still under investigation. Besides, some difficulties also hinder the development of clinical trials of tinnitus. Then, we discussed several major challenges in pharmacological researches of tinnitus and the corresponding development prospects.

Firstly, due to the complete subjectivity of symptoms, there is an absence of objective standardized assessment tools for subjective tinnitus, leading to subjective bias in trial results concerning efficacy of the investigated drug. The current assessment of tinnitus severity mostly relies on tinnitus-related questionnaire scales such as the THI scale, and physicians usually evaluate tinnitus severity, treatment outcome, and prognosis by these scale scores [10,86]. However, these assessment tools lack objective criteria and are completely based on the perception of patients. Therefore, because of the influence of subjective consciousness, emotion, age, education level, response ability and behavioral cooperation of patients, the same medication intervention gets different feedback at different subjects [87]. We believe that further development of investigations on the pathophysiology of subjective tinnitus can partially reflect the objectivity of tinnitus.

Secondly, the etiology of tinnitus is various [38], which includes both otogenic one as well as non-otogenic one. Moreover, otogenic causes include external ear lesions, middle ear lesions, cochlear lesions, retrocochlear lesion and auditory center lesions. Non-otogenic causes include vascular lesions, myoclonus, etc. Complex causes lead to difficulty in treatment [3]. Besides, since tinnitus is multifactorial and heterogeneous, clinical studies on the same drug cannot get a consistent view sometimes, hindering the development of therapeutic research. For example, as mentioned above, memantine did not improve tinnitus in the research while its analog neramexane showed significant effectiveness in another cohort study. At present this phenomenon can be explained by nothing except the multifactorial nature of tinnitus [38]. Therefore, we believe that future studies are expected to group patients according to etiology to determine pharmacological efficacy of NMDAR antagonists for tinnitus with a certain etiology.

Thirdly, Chronic tinnitus symptoms often show a repeated cycle of remission-recurrence with a long treatment period, and some patients have a low willingness to cure tinnitus. Therefore, there are a large

number of cases lost to follow-up in the clinical practice, which causes loss to follow-up biases in cohort studies of tinnitus and then adversely impacts the development of clinical studies, especially observational studies [38]. In order to improve patients' willingness to cooperate with the treatment and cure tinnitus, otologists should not only strengthen the education for them, but also make progress in the therapeutic regimens aiming at shortening the treatment cycle, reducing the side effects of treatment, and eliminating tinnitus-evoked distress more efficiently.

Additionally, the mechanisms by which various NMDAR antagonists exert their effects remain incompletely understood. Many pharmacological agents targeting NMDARs function as allosteric modulators, which can either enhance receptor activity as positive allosteric modulators (PAMs) or suppress it as negative allosteric modulators (NAMs). For instance, spermine and spermidine exhibit concentration-dependent modulation of NMDARs: at low concentrations, they act as PAMs by binding to the polyamine regulatory site, thereby increasing the receptor's affinity for glutamate and glycine and enhancing channel opening probability [88]. Spermine, in particular, can also partially alleviate the voltage-dependent Mg^{2+} block of NMDARs. In contrast, at higher concentrations, these polyamines can directly block the channel, functioning as NAMs. Moreover, polyamine metabolites such as hydrogen peroxide may oxidatively modify NMDAR subunits—for example, by targeting cysteine residues on GluN2A—thereby inhibiting receptor function. Importantly, spermine and spermidine may also exert subunit-specific bidirectional effects: GluN2B-containing NMDARs appear more responsive to positive modulation, whereas GluN2A-containing NMDARs are more susceptible to inhibition [89]. Similar bidirectional modulation has been suggested for other NMDAR antagonists, including nitric oxide, memantine, and ketamine [90–92]. These agents may exhibit variable effects depending on their concentration, the subunit composition of the targeted NMDARs, and the cellular or synaptic context in which they act. Such variability could help explain the inconsistent outcomes observed across different tinnitus clinical trials involving the same NMDAR antagonist.

However, the precise mechanisms by which these antagonists allosterically modulate NMDARs within the auditory system remain poorly characterized. Future pharmacological studies should aim to determine the optimal dosage ranges and identify the specific NMDAR subunit variants most relevant to tinnitus pathology. This approach may enhance the efficacy and specificity of NMDAR-targeted therapies for tinnitus and reduce discrepancies in clinical outcomes.

Tinnitus patients often necessitate a comprehensive and multifaceted treatment approach to address a constellation of issues, including hearing loss, auditory hypersensitivity, anxiety, and cognitive deficits [10]. The etiology of tinnitus is complex and frequently intertwined with a myriad of physiological and psychological factors, rendering a singular pharmacotherapeutic strategy often ineffective. Pharmacological interventions, such as NMDAR antagonists, may serve as a component of a holistic treatment plan or exert therapeutic effects for specific subtypes of tinnitus.

Initially, hearing loss is one of the critical factors contributing to tinnitus. A significant proportion of tinnitus patients concurrently experience hearing impairment, which not only hinders daily communication but may also exacerbate tinnitus symptoms. The utilization of hearing aids can assist in improving hearing acuity, consequently reducing the perceived intensity of tinnitus. Hearing aids amplify environmental sounds, which can partially mask tinnitus and mitigate patients' distress [93]. Furthermore, auditory hypersensitivity or hyperacusis (i.e., excessive sensitivity to normal environmental sounds) frequently coexists with tinnitus. This condition can elicit discomfort or even pain in response to sounds. Therefore, treatment modalities should incorporate sound therapy or desensitization training to facilitate patients' gradual adaptation to the presence of environmental sounds [9].

Additionally, psychological factors such as anxiety and depression are highly prevalent among tinnitus patients. The persistent presence of tinnitus itself can precipitate psychological stress, perpetuating a vicious cycle. Consequently, psychological interventions such as cognitive behavioral therapy (CBT) have demonstrated efficacy in alleviating tinnitus-related anxiety and depressive symptoms. CBT assists patients in modifying their cognition and response to tinnitus, thereby attenuating its impact on quality of life. Lastly, cognitive function deficits pose a challenge for a subset of tinnitus patients [94]. The continuous noise generated by tinnitus can interfere with attention and memory functions. This necessitates addressing through cognitive training and other supportive therapies to aid patients in better coping with the cognitive burden [12,13].

In conclusion, the management of tinnitus necessitates a multidisciplinary and comprehensive approach. It encompasses multiple facets such as sound therapy, cognitive behavioral therapy, physical therapy, pharmacotherapy, and hearing aids. Personalized treatment plans should be formulated based on the etiological factors and concomitant symptoms of tinnitus to holistically ameliorate patients' symptoms and quality of life. This integrated treatment strategy not only targets the overt symptoms of tinnitus but also addresses its underlying physiological and psychological factors, thereby providing more effective long-term management.

Investigation of pharmacotherapeutic strategies for tinnitus constitutes an essential component of comprehensive tinnitus treatment. Compared to other treatment modalities, it may offer advantages such as rapid symptom alleviation and targeting the root causes of the disorder. We believe that NMDAR antagonists exert therapeutic effects for specific subtypes of tinnitus and can serve as a crucial element of a comprehensive tinnitus treatment plan.

6. Conclusion

NMDARs play a critical role in excitotoxicity and neural plasticity within the auditory pathway, contributing to tinnitus development. While non-potent NMDAR antagonists have demonstrated good tolerability and safety, current evidence remains insufficient to support their approval as clinically recognized treatments for tinnitus.

CRediT authorship contribution statement

Chenhao Che: Writing – original draft, Investigation, Data curation. **Yongzhen Wu:** Writing – review & editing, Supervision, Conceptualization. **Shan Sun:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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