Review

Neurotransmitter Modulation Relates with Tinnitus Signal Generation and Management

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Abstract Tinnitus is a subjective perception of phantom sound that currently cannot be objectively measured. However, there is growing evidence suggesting that the biological source of tinnitus may exist in one or more than one place in the auditory pathway. Recent studies have found that neurotransmitters or modulators, such as glutamate, γ-aminobutyric acid(GABA), serotonin, dynorphin, dopamine, neurosteroid, acetylcholine(ACh) and substance P, are involved in tinnitus generation. Animal and human studies have shown that some of these neurotransmitters and the agonists or antagonists of their receptors either affect tinnitus behaviors or demonstrate some degree of treatment effects on tinnitus. However, due to the unclear biological mechanisms of tinnitus and side effects of these drugs, the value of clinical usage of such drugs in treating tinnitus is yet to be established. Revealing the relationship between tinnitus and neurotransmitter receptor functions will help identify more effective drugs for tinnitus treatment. This article reviews the literature of neurophysiological studies on tinnitus in both animal and human subject studies at various levels of the auditory pathway.

Key words tinnitus; auditory system; NMDA; serotonin; GABA; ACh

Introduction

Tinnitus is assessed based on patient's subjective description rather than pathological source due to the lack of knowledge of its mechanisms and available objective measurement. However, there is growing evidence suggesting that tinnitus is more than a psychological hallucination. It has one or more than one physiologic source in the auditory pathway and/or in other parts of the central nervous system. Although it is still not clear where tinnitus is located, e.g., in the ear or in the brain, in the auditory system or in non-auditory systems, significant progress has been made in the past ten years that links tinnitus with neurological changes in the brain. Since neurotransmitter release from neuron presynaptic structures and the response in postsynaptic structures play an important role in auditory signal generation, transmission and perception, dysfunction of certain neurotransmitters and their receptors may be a key in triggering tinnitus generation. Localizing the origin and cause of tinnitus using neurophysiological approach has become a critical issue in finding a treatment of tinnitus to help millions of patients who suffer from tinnitus. The goal of this paper is to summarize recent findings on neurotransmitters and neurotransmitter receptors related to tinnitus mechanisms and treatment.

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Glutamate Receptor

Glutamate is one of the most important excitatory neurotransmitters in both peripheral and central nervous systems. In the inner ear, glutamate is released by hair cells and received by the dendrites of afferent spiral ganglion neurons through two different types of neurotransmitter receptors, non-NMDA and NMDA receptors[1]. These two receptors work as a dual receptor system. Non-NMDA receptors include the kainic acid subtype and the AMPA subtype and probably contribute to the fast response of spiral ganglion neurons. NMDA receptors are likely involved in a slow effect[2]. A peripheral tinnitus model suggests that a typical pattern of depolarization of the afferent nerve depends on the balance of the normal synaptic function. Inner ear

diseases, such as presbycusis, sudden hearing loss and noise-induced hearing loss, may involve dysfunction of cochlear-synaptic functions, causing an increase in spontaneous neuronal activities. Evans found that administration of salicylate increased spontaneous discharges of auditory nerves in cats[3, 4]. The increased spontaneous activity of afferent nerves was suggested to be a physiological source of tinnitus. Based on this hypothesis, Ehrenberger et al studied the effect of caroverine(a calcium channel blocker and antagonist of AMPA and NMDA receptors) on tinnitus in animal models[5, 6, 7]. They found that applying caroverine on the round window exhibited a statistically significant protective action in noise-induced hearing loss and tinnitus. However, Muller et al studied salicylate effects on auditory nerve activity in gerbils and found that spontaneous activities in auditory nerves were significantly decreased or remained unchanged after salicylate injection. They concluded that the salicylate-induced increasing activities in the central auditory system were not caused by cochlear nerve hyperactivity[8]. The peripheral tinnitus model therefore cannot fully explain the causes of tinnitus.

GABA Inhibition

The central tinnitus model is based on the plasticity change of the central auditory system in response to peripheral damage. GABA, a major inhibitory neurotransmitter in the central auditory pathway, plays an important role in processing acoustic stimuli[9] and in central reorganization after peripheral damage[10, 11, 12]. Cochlear damage induced by noise exposure or aging can cause a decrease in glutamic acid decarboxylase (GAD) expression, an enzyme for GABA synthesize, in the cochlear nucleus(CN) and the inferior colliculus (IC)[13, 14, 15]. GABA concentration changes can affect auditory signal processing including tuning curve, filtering, masking and amplification in the central auditory system. Syka reported that acute noise exposure induced an increase of middle latency responses recorded from the auditory cortex (AC) which might be related to damage of the GABA inhibitory system[16]. Suneje et al found a depressed GABA release several days after bilateral removal of the ossicles and elevated GABA release 4 months after middle ear removal[12]. Bauer et al studied GAD expression and binding characteristics of GABA-A receptors in the auditory brainstem in rats after tinnitus was induced by salicylate[17]. They found a significant elevation of GAD levels in the IC in rats showing tinnitus behavior, presumably to compensate GABA reduction. They also found that the number of GABA-A binding sites decreased significantly in rats with tinnitus. These studies suggest a connection between decreased inhibitory activity and tinnitus behavior. Based on the plasticity hypothesis, studies aimed at increasing GABA inhibition in the central auditory system to reduce tinnitus have been conducted in animal models. Administration of baclofen, a GABA-B receptor agonist, resulted in a blocking effect on amplitude enhancement in the IC induced by noise exposure[18]. Vigabatrin, a GABA receptor agonist used for treating epilepsy, was found to suppress noise-induced tinnitus in rats[19]. However, in a recent human subject study, gabapentin, which has a similar chemical structure as GABA and is also used for treating epilepsy, failed to show a sufficient effect on reducing tinnitus[20]. This leads to the assumption that tinnitus can arise from multiple sources and involve more than one neurotransmitter such as GABA.

Serotonin (5-HT) Expression

Serotonin is a neurotransmitter broadly expressed in the central nervous system and affects a wide range of biological and behavioral functions, such as emotions, anxiety and stress. As stress and anxiety are common symptoms in tinnitus patients, the role of serotonin in persistent distressing tinnitus has been studied in order to develop an effective pharmacological intervention to ameliorate tinnitus. Studies have found that patients who are under stress normally show a low level of serotonin concentration in blood samples and that increasing serotonin level by taking serotonin reuptake inhibitor types of drugs lessens symptoms in some patients[21]. Sachanska et al. tested blood serotonin concentration in patients with and without tinnitus[22]. They found that tinnitus patients showed significantly higher serotonin values in their blood than those without tinnitus[22]. In animal studies, Liu et al. found that salicylate(350 mg/kg, i.p.) induced a dramatic increase of serotonin levels in both the IC and the AC. They also found exceeding levels of glucose and lactate, suggesting an increase of neuronal activity in the brain[23]. This study implies that increased serotonin levels induced by salicylate may relate to neuronal activity changes and tinnitus. This may explain why some antidepressant drugs, most of them serotonin reuptake inhibitors, may provoke or

worsen tinnitus rather than lessen it[24]. The relationship between tinnitus and stress and the role of serotonin expression in these conditions need to be clarified.

Dynorphin, Dopamine and Efferent Systems

Inner ear excitation is largely generated by inner hair cells(IHC) and carried to the central auditory system by afferent nerves. The afferent neuronal activity is modulated by the lateral efferent system through the release of various neurotransmitters, such as dynor- phins[25, 26] and dopamines[27, 28]. Dynorphins are a class of peptides produced by a variety of neurons and primarily works as an agonist on opioid receptors. Extreme anxiety or stress can stimulate widespread release of endogenous dynorphins which in turn exert an extensive range of physiologic and behavioral effects[29, 30]. Excessive amounts of dynorphins can be released from the lateral efferent axons into the synaptic region underneath inner hair cells in the cochlea during intense noise exposure[26, 30]. The presence of dynorphins can either increase IHC's spontaneous release of glutamate or enhance the response of NMDA receptors to glutamate, which has been hypothesized to be related with tinnitus generation. However, in neurons in the trigeminal and hippocampus nuclei, dynorphins have been shown to have both enhancement and suppression effect on NMDA receptors[31, 32, 33]. The direct effects of dynorphins on NMDA receptors in the cochlea have yet to be studied.

Dopamine also shows a modulating effect on IHC depolarization and on spiral ganglion neuron firing properties. In human studies, administration of dopamine receptor antagonists, such as sulpiride and melatonin, reduces tinnitus perceptions. In a clinical study which involved 120 patients, tinnitus perception was reduced by 56% by administration of sulpiride, 40% by melatonin administration, and 81% by sulpiride plus melatonin[34]. However, since there is not objective measurement of tinnitus, a strong placebo effect has been found in tinnitus treatment. The efficacy of these drugs needs to be confirmed. Dopamine receptors are also expressed in the central auditory system. The effects of dopamine antagonist on central system should be also evaluated[35].

Mineralocorticoid Receptors and Neurosteroid

Neurosteroids, which are synthesized in the central nervous system, exert a wide range of effects on memory, behavior and neuroprotection. Neurosteroids, such as pregnenolone and dexamethasone, have been used in clinical treatment of inner ear diseases, such as sudden sensorineural hearing loss[36, 37], Meniere's disease[38, 39] as well as tinnitus[40, 41, 42, 43]. However, the effect of steroid treatment on tinnitus is far from consistent. Sakata conducted a retrospective study on the transtympanic dexamethasone treatment on tinnitus and found that application of 2-4 mg dexamethasone on the round window showed a positive effect on the patients who had low-pitched tinnitus, but little effect on those with high pitched tinnitus[43]. Some studies have suggested that steroid effect in the inner ear is mediated by mineralocorticoid receptors since the effect of neurosteriod can be blocked by spironolactone, a mineralocorticoid receptor antagonist[44]. As some neurosteroid receptors, e.g., glucocorticoid and mineralocorticoid receptors, are widely expressed in the inner ear on spiral ganglion neurons, organ of Corti and spiral limbus[45, 46], pharmacologic treatments that selectively target mineralocorticoid receptors may prove to be a better treatment option that can provide clinical benefits while avoiding side effects from neurosteroid treatment[44].

Neurosteroids have also shown a neural protecting effect in the cochlea in response noise exposure. After the exposure to loud noise, administration of mifepristone elevated the compound action potential amplitude significantly compared to saline treatment[47, 48]. The effects of mifepristone presumably involve blocking cell death following noise exposure through glucocorticoid receptors expressed in IHCs and afferent nerve fibers. The neural pathway of neurosteroids in protecting cell death is still not clear. One hypothesis is the role played by the stria vascularis. Steroids affect maintenance of normal cochlear fluid homeostasis by secreting potassium into the endolymph. Prednisolone, hydrocortisone or dexamethasone cause an increase of current density in isolated stria vascularis in a dose-dependent manner by increasing the secretion of potassium[49]. This can conceivably account for some of the physiological and clinical effects of neurosteroids on inner diseases and tinnitus.

Cholinergic Receptors and Cochlear Nucleus Activity

Kaltenbach et al reported that intense sound exposure induced an increase in spontaneous activity in the dorsal cochlear nucleus(DCN)[50-53]. This evidence has

been used as an important etiological factor in the CN for tinnitus generation. Their studies also suggest that noise exposure-induced hyperactivity in the CN is related with the cholinergic modulation change in the DCN as a result of both changes in cholinergic inputs and cholinergic receptors[54]. Jin et al reported that the average choline acetyltransferase activity increased significantly in the DCN on the exposed side. Application of carbachol, a cholinergic agonist, on DCN surface induced a decrease in spontaneous activity in fusiform cells. The suppression induced by carbachol was considerably stronger in sound exposed animals than the control animals, suggesting an association between sound exposure-induced increase in spontaneous activities and upregulation of cholinergic receptors expression in the DCN [55].

Cholinergic changes can also affect other part of the central auditory system, since cholinergic nerves and their receptors are expressed in the thalamus and the AC [56]. Cholinergic neuron activities show a broad effect on auditory physiological and behavioral responses, such as auditory attention, memory and learning. Damage of the cholinergic neuron or its receptors can induce a variety of behavioral deficits and may be related to tinnitus and other central auditory processing disorders. In the AC, cholinergic neurotransmitter receptors are expressed together with other neurotransmitters including glutamate and GABA. Excitation of cholinergic neurons shows a strong modulating effect on glutamate and GABA release. Thus, damage of cholinergic neurons or their receptors can affect glutamate and GABA functions. Recent studies have shown that scopolamine, a cholinergic receptor antagonist, suppresses salicylate-induced plasticity change in the AC [57]. In our pilot studies, scopolamine is also shown to suppress salicylate-induced tinnitus behavior in rats (unpublished).

Substance P and Pain Receptors

There are many analogies between phantom pain and tinnitus. Like tinnitus, pain is a subjective perception and the amount of pain is difficult to quantify [58]. Pain can arise from a great variety of lesions and no specific mechanism for the perception has been identified. Chronic pain is often a consequence of a peripheral injury, but the injury itself may not account for the sustained nature of the chronic pain. The peripheral damage may induce a persistent central change even after the acute injury has resolved, which we often name as a plasticity change in the central nerve system-although the location, pathology of this central change are often not known[59].

Several neurotransmitters and their receptors are related to pain. One of the important pain-related peptides is substance P, which is broadly expressed in the peripheral and central nervous systems. Recent studies on neurokinin-1 receptor(NK1, substance P receptor) gene knock- out mice suggested that substance P has an important and specific role in the central nociceptive and peripheral inflammatory responses to noxious stimuli that evoke neurogenic inflammation [60]. In the peripheral nervous system, substance P is involved in the development of inflammatory pain hypersensitivity in spinal cord neurons, showing a decreased threshold for action potential firing and increased responsiveness to a given stimulus[61, 62]. In the central nervous system, substance P contributes to seizures, hippocampal excitability, etc [63, 64]. NK1 antagonists have been tested for therapeutic targets in different types of pain, including dental pain (toothache), osteoarthritis, neuropathic pain and migraine[65]. Since the mechanism involved in pain has been implicated in tinnitus, substance P and its receptors may also be involved in tinnitus gener-ation [66].

Substance P has been identified in a number of structures in the cochlea and vestibular system, including hair cells, spiral ganglion cells and cochlear vessels [67-69]. Substance P can modulate cochlear function through neurokinin receptors. Perilymphatic perfusion of substance P methyl ester(SPME), a SP receptor agonist, produces a dose-dependent increase in the amplitude of the compound action potential, whose effects are blocked by SP antagonists [70]. This suggests that SP may modulate the activity of type I spiral ganglion neurons through NK1 receptors. Substance P may also play a role in hyperalgesia and tinnitus. Changes of substance P agonists and antagonists in spiral ganglion neural activity can lead to hyperactivity in the auditory nerve, one of the putative mechanisms of cochlear tinnitus[4, 50]. One pathway of substance P that may be involved in tinnitus, vertigo, and hearing deficits associated with basilar artery migraine headaches is aberrant trigeminal nerve activity [71]. However, the mechanism of substance P in tinnitus and other inner ear diseases is still not clear.

In conclusion, significant progress has been made

in the past ten to fifteen years regarding tinnitus mechanism and treatment. Various neurotransmitters and their receptors have been found to be involved in tinnitus generation. Such findings provide the hope of developing effective tinnitus treatment using pharmacological agents interacting with these neurotransmitters and their receptors. Neurophysiologic studies aimed at locating the source and pathologic mechanisms of tinnitus will be critical to finding the solution for this common illness.

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