Sympathetic Nervous System Regulation of Auditory Function

Chaoyong Tian Dingjun Zha

Department of Otolaryngology Head and Neck Surgery, Xijing Hospital, Fourth Military Medical University, Xi'an, China

Keywords

Adrenaline · Autonomic nervous system · Cochlea · Hearing disorders · Noradrenaline

Abstract

Background: The auditory system processes how we hear and understand sounds within the environment. It comprises both peripheral and central structures. Sympathetic nervous system projections are present throughout the auditory system. The function of sympathetic fibers in the cochlea has not been studied extensively due to the limited number of direct projections in the auditory system. Nevertheless, research on adrenergic and noradrenergic regulation of the cochlea and central auditory system is growing. With the rapid development of neuroscience, auditory central regulation is an extant topic of focus in research on hearing. **Summary:** As such, understanding sympathetic nervous system regulation of auditory function is a growing topic of interest. Herein, we review the distribution and putative physiological and pathological roles of sympathetic nervous system projections in hearing. **Key Messages:** In the peripheral auditory system, the sympathetic nervous system regulates cochlear blood flow, modulates cochlear efferent fibers, affects hair cells, and influences the habenula region. In central auditory pathways, norepinephrine is essential for

plasticity in the auditory cortex and affects auditory cortex activity. In pathological states, the sympathetic nervous system is associated with many hearing disorders. The mechanisms and pathways of sympathetic nervous system modulation of auditory function is still valuable for us to research and discuss.

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Introduction

Sympathetic efferent pathways form a component of the autonomic nervous system. Sympathetic nerve postganglionic fiber neurotransmitters predominantly comprise norepinephrine (NE), adrenaline, acetylcholine, purine, and polypeptides. Adrenergic receptors (ARs) regulate the functional effects of NE and adrenaline. Three types of ARs exist: $\alpha 1$, $\alpha 2$, and β . These ARs belong to the G protein-coupled receptor superfamily. Each AR comprises 3 subtypes: $\alpha 1a$, $\alpha 1b$, and $\alpha 1d$; $\alpha 2a$, $\alpha 2b$, and $\alpha 2c$; and $\beta 1$, $\beta 2$, and $\beta 3$. The ARs are widely present across the peripheral and central auditory pathways (shown in Table 1) [Sutin and Minneman, 1985; Boyajian et al., 1987; Wanaka et al., 1989; Carrasco et al., 1990; Gjedde et al., 1991; Martin et al., 1994; Ebert, 1996; Day et al., 1997; Domyancic and Morilak, 1997; de Minteguiaga et al.,

Table 1. Summary of studies of ARs in the peripheral and central auditory pathways

AR	Species	Peripheral auditory system	References	Species	Central auditory pathways	References
α_1	ACI Black Agouti rats	Organ of Corti, SGNs	[Khan et al., 2007]	Rat Mice Sprague-Dawley rats Rat Rat	Cochlear nucleus Inferior colliculus Auditory cortex Auditory cortex Auditory cortex	[Ebert, 1996] [Williams et al., 2020] [Salgado et al., 2012] [Sutin and Minneman, 1985] [Gjedde et al., 1991]
α_{1a}	Gerbils	Spiral modiolar artery	[Gruber et al., 1998]	Sprague-Dawley rats Mouse	Ventral cochlear nucleus Inferior colliculus	[Domyancic and Morilak, 1997] [Papay et al., 2006]
α_{1b}						
α_{1d}				Sprague-Dawley rats	Inferior colliculus	[Day et al., 1997]
α_2	Rat Mongolian gerbils Rat Gerbils Rat	Cochlea, vestibular labyrinth Modiolus vessels SGNs Stria vascularis SGNs	[Cai et al., 2013b] [Carrasco et al., 1990] [Zha et al., 2007] [Martin et al., 1994] [Cai et al., 2013a]	Rat Mouse Rat Zebra finch Sprague-Dawley rats	Cochlear nucleus Ventral cochlear nucleus-LSO Inferior colliculus Auditory cortex Auditory cortex	[Ebert, 1996] [Hirao et al., 2015] [Boyajian et al., 1987] [Ikeda et al., 2015] [Salgado et al., 2012]
α_{2a}				Mice Rat	Inferior colliculus Auditory cortex	[Williams et al., 2020] [Winzer-Serhan and Leslie, 1999]
α_{2b}						
α_{2c}						
β	Rat	Stria vascularis	[Ishii et al., 2000]	Gerbils	Auditory cortex	[Schicknick et al., 2019]
	Gerbils	Stria vascularis	[Schicknick et al., 2019]	Rat	Inferior colliculus, the nucleus of the lateral lemniscus and the cochlear nuclei	[Wanaka et al., 1989] [Salgado et al., 2012] [Sutin and Minneman, 1985]
β_1	ACI Black Agouti rats Gerbils	Auditory nerve, nonstrial lateral wall Strial marginal cells, inner and OHCs, outer sulcus, and spiral ganglia cells of the cochlea. Dark, transitional, and supporting cells of the vestibular labyrinth	[Khan et al., 2007] [Fausser et al., 2004]			
	Human	Endolymphatic sac	[Kim et al., 2017]			
β_2	Gerbil ACI Black Agouti rats Human Long-Evans rats	Nonstrial lateral wall Auditory nerve, nonstrial lateral wall Endolymphatic sac Stria vascularis	[Schimanski et al., 2001] [Khan et al., 2007] [Kim et al., 2017] [De Minteguaga et al., 1998]	Mice	Inferior colliculus	[Williams et al., 2020]
β_3						

ARs, adrenergic receptors; SGNs, spiral ganglion neurons; LSO, lateral superior olive; OHCs, outer hair cells.

Fig. 1. Schematic of sympathetic nervous system modulation of hearing. Afferent auditory pathway projections are indicated by black, blue, red, and green arrows. Olivo-cochlear bundle is indicated by a gray arrow. Putative projections or regulation by the sympathetic nervous system are indicated by purple arrows.

1998; Gruber et al., 1998; Winzer-Serhan and Leslie, 1999; Ishii et al., 2000; Schimanski et al., 2001; Fauser et al., 2004; Papay et al., 2006; Khan et al., 2007; Zha et al., 2007; Salgado et al., 2012; Cai et al., 2013a, b; Hirao et al., 2015; Ikeda et al., 2015; Kim et al., 2017; Schicknick et al., 2019; Williams et al., 2020] and are positioned to affect auditory and vestibular processing.

The regulation of peripheral and central auditory pathways by the sympathetic nervous system has been reported [Foote et al., 1975; Chikamori et al., 1980; Kossl and Vater, 1989; Laurikainen et al., 1993; Ren et al., 1993a, b; Manunta and Edeline, 1997, 1999, 2004; Edeline et al., 2011; Martins and Froemke, 2015]. In the periphery,

sympathetic nerves mainly regulate cochlear blood flow (CBF) [Spoendlin and Lichtensteiger, 1966; Spoendlin, 1981; Laurikainen et al., 1993; Ren et al., 1993a, b]. Centrally, the key roles of locus coeruleus (LC)-NE on auditory pathways are predominantly inhibitory [Foote et al., 1975; Chikamori et al., 1980; Kossl and Vater, 1989; Manunta and Edeline, 1997, 1999]. In pathological states, dysfunction of the sympathetic nervous system may lead to auditory disorders. Modulation of the auditory system by the sympathetic nervous system is complex. Understanding this relationship is of high clinical significance. For example, a mechanism was reported that demonstrated a vessel associated with sympathetic led to cochle-

ar vasoconstriction and exacerbated noise-induced cochlear damage [Hildesheimer et al., 1991].

In this review, we highlight the key roles of the sympathetic nervous system in auditory function. First, we focus on the relationship between sympathetic activity and peripheral auditory processes, followed by an evaluation of the relationship between sympathetic activity and central auditory pathways. Finally, we summarize research on sympathetic nervous system modulation of auditory disorders. This review provides timely insight into the mechanisms underpinning sympathetically related auditory dysfunction to guide future research in this area.

Sympathetic Activity and Peripheral Auditory System

The peripheral auditory system (shown in Fig. 1) consists of the external ear, middle ear, inner ear, and auditory nerve. In mammals, the peripheral auditory system receives extensive adrenergic innervation from the sympathetic nervous system, particularly from the superior cervical ganglia (SCG) and stellate ganglion (SG). Tyrosine-hydroxylase-immunoreactive nerve fibers are expressed in most regions of the middle ear mucosa, and these fibers are close to small-caliber vessels [Uddman et al., 1983; Nagaraj and Linthicum, 1998]. The sympathetic nervous system projecting into the inner ear comprises 2 main components [Spoendlin and Lichtensteiger, 1967; Spoendlin, 1981; Hozawa and Kimura, 1990]: a vessel-associated component originating from the SG bilaterally and a dense plexus forming around the major arteries, and a vessel-independent component originating ipsilaterally from the SCG producing multiple terminals in the osseous spiral lamina region, which contains the cell bodies and axons of cochlear nerve fibers [Spoendlin and Lichtensteiger, 1966; Borg et al., 1974; Densert and Flock, 1974]. The functional significance of cochlear adrenergic innervation includes its roles in the regulation of blood flow volume, and in the control the metabolism of inner hair cells (IHCs), and outer hair cells, as well as efferent and afferent axons [Densert, 1974].

The blood supply to the cochlea originates from the common cochlear artery, which includes the spiral modiolar and vestibulocochlear arteries. The regulation of CBF by the sympathetic nervous system and ARs is well established. Sympathetic innervation influences vascular tone. By regulating arteriole diameter, the vessel-associated component has a significant effect on CBF [Brechtelsbauer et al., 1990; Laurikainen et al., 1993, 1997; Ren

et al., 1993b]. Disruption of the sympathetic nervous system partially abolished, found that sympathetic activation contributes to sound-induced reduction of CBF [Burwood et al., 2020]. Unilateral and bilateral SG blockade resulted in effects of differing magnitude on CBF on each side, although both resulted in an increase in CBF. In contrast, electrical stimulation of the SG reduced CBF [Laurikainen et al., 1993]. Stimulation of the SCG decreased ipsilateral CBF. However, superior cervical ganglionectomy did not have any significant effect on tonic CBF levels [Laurikainen et al., 1997]. ARs regulate the function of the cochlea and influence CBF [Ren et al., 1993b]. In the vascular system of the cochlea, $\alpha 1$ - and $\alpha 2$ -ARs are differentially distributed and are involved in CBF regulation; these differences are underpinned by interspecies variations [Carrasco et al., 1990; Ohlsen et al., 1991; Laurikainen et al., 1994; Gruber et al., 1998]. AR subtypes are differentially distributed in the cochlea. For instance, $\alpha 1$ -ARs are expressed in the organ of Corti and spiral ganglion (regions unrelated to vasculature), $\beta 1$ -ARs are expressed in nerve fibers beneath IHCs, and $\beta 2$ -ARs are expressed in nerve fibers crossing the habenula perforate and project to IHCs [Khan et al., 2007]. Pharmacological approaches have been utilized to elucidate the functional neuroanatomy of $\alpha 2$ -ARs in the mammalian cochlea, such as in modiolus vessels [Carrasco et al., 1990], spiral ganglion neurons (SGNs) [Zha et al., 2007], and stria vascularis [Martin et al., 1994]. Ishii et al. [2000] reported that cells constituting the stria vascularis may express β -ARs. Nonstrial lateral wall tissues express $\beta 1$ - and $\beta 2$ -ARs, but the $\beta 2$ -AR is the predominant functional receptor subtype [Schimanski et al., 2001]. Khan et al. [2007] provided strong evidence that ARs are expressed in the SGNs and organ of Corti, highlighting a possible mechanism of regulation of peripheral auditory sensory function via adrenergic input [Khan et al., 2007]. Cai et al. [2013b] reported that $\alpha 2$ -ARs were widely distributed in various areas and the cellular sites of $\alpha 2$ -ARs vary between different cell subtypes, AR subtypes, and time-points. After that, Cortada et al. [2017] reported that brimonidine, acting directly via $\alpha 2$ -ARs, protects hair cells from gentamicin-induced toxicity. At the same time, a report by Inamoto et al. [2017] demonstrated that the isoproterenol (a β -AR agonist)-induced maximum change in endolymphatic hydrostatic pressure in the ampulla was significantly smaller than in the cochlea. However, another investigation provided functional evidence for the involvement of $\beta 1$ - and $\beta 2$ -ARs in apical electrogenic ion transport in human endolymphatic sac epithelium [Kim et al., 2017].

Responses of the vessel-independent component close to the habenula perforated to noise and its role in cochlear homeostasis are unclear. Electrical stimulation of the sympathetic trunk with superior cervical ganglionectomy increased N1 wave amplitude of compound action potentials (CAPs) to 15–20%. Increased variability in N1 wave amplitude after sympathetic stimulation has been reported [Pickles, 1979; Lee and Møller, 1985]. In animal experiments, changes in N1 wave amplitude produced different results. Compared to high SCG stimulus intensities, low SCG stimulus intensities caused a greater increase in latency of the N1 response [Lee and Møller, 1985]. The dynamic range of CAP was smaller after a unilateral cervical sympathectomy compared to that in nonsympathectomized cochleas [Hultcrantz et al., 1982]. In conclusion, these findings indicate a regulatory role of SCG fibers on afferent auditory nerve signals, although the magnitude of its effects remains uncertain. Perlman and Kimura [1955] reported that sympathetic stimulation did not affect blood flow of the stria vascularis. NE may affect the permeability of the spiral modiolar artery. However, this area contains extensive terminals, and modulation of permeability is unlikely to be the only physiological function of this extensive innervation. One factor that should be considered is that catecholamines may exert direct effects on outer and IHC metabolism. Zha et al. [2007] reported that NE input to SGNs may modulate auditory transmission by influencing GABA responses. Early physiological studies have shown that sympathetic fibers affect the latency and/or amplitude of the auditory nerve CAP N1 wave, highlighting sympathetic modulation of afferent nerve function, although consistent explanations of the underlying mechanism are lacking [Pickles, 1979; Muchnik et al., 1983; Lee and Møller, 1985]. Wangemann and Wonneberger [2005] reported that sympathetic innervation led to vasoconstriction of the main blood supply of the cochlea in guinea pigs and gerbils. Conversely, SG block improved the hearing parameters of normal CBF in rats [Firat et al., 2008]. The decrease in CBF was significantly greater following propofol infusion with topical epinephrine compared to that following control treatment, and the threshold was increased [Jang et al., 2016]. These findings highlight potential avenues for clinical investigation. Notably, the cochlear sympathetic system is associated with age and sex [Vicente-Torres and Gil-Loyzaga, 2002].

The cochlea receives 2 categories of efferent nerve fibers, including the lateral and medial olivocochlear efferent fibers. Lateral olivocochlear fibers contact type 1 auditory nerve dendrites below IHCs, and medial olivocochle-

ar fibers contact the outer hair cells. Alongside olivocochlear efferent fibers, the cochlea also receives sympathetic adrenergic efferent fibers. Morphological research suggests a sympathetic role in the habenula region, where afferent axons have lost their myelin sheaths. Just below the basilar membrane of the nerve bundles, adrenergic nerve terminals and prominent groups of terminals are regularly observed around the nerve bundles. This is the location where action potentials are meant to be generated. NE released in this area may affect the threshold for nerve impulse initiation [Densert, 1974]. Mulders and Robertson [2000] suggested a direct input to medial olivocochlear neurons from NE-containing neural pathways. They observed an excitatory action of NE on both medial and lateral olivocochlear neurons. These results indicate that noradrenergic inputs can regulate cochlear efferent functions [Mulders and Robertson, 2005]. Otherwise, adrenergic regulation of neural/supporting cell function within the organ of Corti is a novel identified mechanism that may influence afferent signaling [Khan et al., 2007]. Nevertheless, the modulatory mechanisms underpinning these processes remain unclear.

Sympathetic Activity and Central Auditory Pathways

The central auditory system (shown in Fig. 1) comprises the dorsal and ventral cochlear nucleus and superior olivary nuclei in the brainstem, lateral lemniscus and inferior colliculus in the midbrain, medial geniculate nuclei of the thalamus, and auditory cortex in the temporal lobe of the cerebral cortex.

In rodents and primates, the neurons that releases NE are located in the brainstem in clusters named A1–A7 [Dahlström and Fuxe, 1964]. Of these, the LC (A6) projects to most regions in the brain [Loughlin et al., 1986], except the basal ganglia [Berridge and Waterhouse, 2003], and is the only source of noradrenergic innervation of the cerebral cortex [Jones et al., 1977; Moore and Bloom, 1979]. Immunohistochemical analyses suggest that the majority of neurons in the LC are noradrenergic [Grzana and Molliver, 1980].

Brainstem noradrenergic neurons comprise a small yet diverse population of cells that project to almost all regions of the central nervous system. In a mature system, these neurons are anatomically subdivided into 6 nuclei: A1, A2, A5, A7, LC, and subcoeruleus. LC plasticity induces changes in auditory cortex responses lasting on the scale of hours and improves auditory perception for days to weeks [Martins and Froemke, 2015]. The selective

plasticity induced in the frequency tuning of auditory cortex neurons by LC stimulation is bidirectional [Edeline et al., 2011]. Noradrenergic innervation of the cochlear nucleus [Andén et al., 1966; Comis and Whitfield, 1968], superior olivary complex (SOC) [Wynne and Robertson, 1996; Woods and Azeredo, 1999; Mulders and Robertson, 2001], and inferior colliculus [Klepper and Herbert, 1991] has been reported and identified to originate in the LC. Mulders and Robertson [2005] reported that a significant component of the noradrenergic innervation of the guinea pig SOC arises in the locus subcoeruleus, and this structure could be the homolog of the LC in other species. The noradrenergic system also innervates neurons in the superior olive that project to the cochlear nucleus [Behrens et al., 2002]. Inhibitory effects were observed in cochlear nucleus neurons of bats and cats during NE iontophoresis [Chikamori et al., 1980; Kossl and Vater, 1989]. The SOC in the rat brainstem comprises many sub-nuclei, including the medial superior olive, lateral superior olive, medial nucleus of the trapezoid body, ventral nucleus of the trapezoid body, and various other less well-defined peri-olivary areas [Harrison and Feldman, 1970; Osen et al., 1984]. It comprises a component of the ascending auditory pathway that receives input from the cochlear nuclei and projects to higher central auditory centers in the brain [Beyerl, 1978; Coleman and Clerici, 1987; Friauf and Ostwald, 1988; Thompson and Thompson, 1993; Kelly et al., 1998; Oliver, 2000]. The lateral superior olive is a brainstem node that receives noradrenergic projections from the LC and is a site where acoustic information is first computed [Woods and Azeredo, 1999; Mulders and Robertson, 2001].

The lateral lemniscus contains dorsal, ventral, and intermediate nuclei. Noradrenergic innervation of the nucleus arises exclusively from an ipsilateral group of neurons scattered among the fibers of the lateral lemniscus. Noradrenergic neurons projecting to the LC and lateral lemniscus area were stimulated 40 ms before delivery of a tactile stimulus to the face, resulting in complete suppression [McBride and Sutin, 1984]. In the A7 LC cell group, numerous dopamine-beta-hydroxylase (DBH) positive neurons were noted within and medial to the lateral lemniscus [Mulders and Robertson, 2001]. However, the function of noradrenergic neurons projecting to these regions is not fully known.

Phenylethanolamine N-methyltransferase is an enzyme that converts NE into adrenaline. In monkeys, distribution of adrenergic innervation of the thalamus indicated a low to moderate density of phenylethanolamine

N-methyltransferase fibers in the medial geniculate nucleus [Rico and Cavada, 1998]. The auditory role of adrenergic innervation and regulation of the medial geniculate nucleus is unknown.

The auditory cortex located in the temporal lobe of the cerebral cortex in monkeys and humans. NE is an important modulator of neuronal activity in the auditory cortex. The effect of LC-NE on central auditory pathways is typically inhibitory. Seminal research [Foote et al., 1975] reported that dose-dependent inhibitory effects of spontaneous and evoked activity were observed following NE application. Inhibitory effects were observed in 35–50% of auditory cortex neurons in rats [Manunta and Edeline, 1997, 1999].

Pairing of auditory stimuli-induced LC plasticity leading to changes in auditory cortex responses and improvements in auditory perception. Selective alterations of a particular sound frequency-induced differential LC plasticity between the cortex and thalamus [Edeline et al., 2011; Martins and Froemke, 2015]. Brief increases in NE concentration-induced selective modifications in the turning curves of cortical neurons. In most situations, the effects are contrary to acetylcholine induction [Manunta and Edeline, 2004]. LC plasticity and NE application may involve different pathways/mechanisms to influence auditory cortex activity. The involvement of NE in critical period modulation remains obscure at present, although recent research has implicated NE in experience-dependent plasticity in the adult auditory cortex [Edeline et al., 2011]. Salgado et al. [2011] reported that NE influences cortical suppression in a layer-specific manner by reducing apical but increasing basal suppression onto layer II/III pyramidal neuron dendrites. In songbirds, NE increases signal detection and information encoding of complex auditory stimuli by inhibitory spontaneous “noise” activity, and these actions are independent of local neuroestrogen synthesis [Ikeda et al., 2015]. NE has a key role in the primary auditory cortex and attention of stressed rats during tone discrimination [Pérez-Valenzuela et al., 2016]. Studies using DBH knockout (*Dbh*^{−/−}) mice and controls in a biased acoustic environment during the auditory cortical critical period revealed that the best frequencies were redistributed in controls but not *Dbh*^{−/−} mice. This suggests that NE is not critical for cortical circuit formation but is essential for plasticity in the auditory cortex during the critical period, demonstrating that NE is necessary for input-dependent plasticity in the developmental auditory pathway [Shepard et al., 2015].

Three AR families are expressed in the brain ($\alpha 1$, $\alpha 2$, and $\beta 1$ – $\beta 3$), which have specific presynaptic and postsyn-

aptic sites and laminar expression patterns throughout the cortex [Berridge and Waterhouse, 2003]. Schicknick et al. [2019] reported that β -adrenergic signaling in the auditory cortex has task-related importance for discrimination learning of complex sounds. To explore the effect of basolateral amygdala β 1-ARs in fear responses, (arachidonylcyclopropylamide, a selective CB1 cannabinoid receptor agonist) was used to modulate CB1Rs. Receptor inactivation resulted in a bidirectional effect on arachidonylcyclopropylamide responses in contextual and acoustic fear conditioning [Nasehi et al., 2018].

Regulation of Sympathetic Nervous System in Hearing Disorders

Autonomic innervation of the inner ear is a research area of increasing interest as many hearing disorders, including tinnitus, vertigo, and sudden deafness may be caused by an autonomic disorder [Seymour and Tappin, 1951; Passe, 1953]. Cochlear ischemia has been associated with many hearing disorders, such as noise-induced hearing loss, age-related hearing loss, sudden sensorineural hearing loss, tinnitus, and Ménière's disease [Perlman et al., 1959; Thalmann et al., 1972; Santi and Duvall, 1978; Ren et al., 1995; Lamm and Arnold, 1996; Nuttall, 1999; Mom et al., 2001; Shi, 2011]. Based on the correlation about sympathetic activity and auditory pathways that we stated above, more and more studies focus on the clinical effects of the sympathetic nervous system in hearing disorders.

Tinnitus

Autonomic nervous system imbalance, which often occurs in patients with tinnitus-triggered stress. One candidate mechanism of tinnitus is hyperarousal caused by enhanced activation of the sympathetic nervous system. A blockade of the superior cervical sympathetic ganglion may be a useful alternative for patients with tinnitus not responding to conventional therapy [Koning et al., 2016]. Noninvasive vagus nerve stimulation reduces sympathetic preponderance in patients with tinnitus [Ylikoski et al., 2017]. Patients with chronic tinnitus received xenon phototherapy of the SG have a significant effect [Shimizu et al., 2018].

Vertigo

Vestibular disturbances associated with the autonomic nervous system [Yates, 1992; Biaggioni et al., 1998; Yates and Kerman, 1998; Yates et al., 2000, 2002; Ray and

Monahan, 2002; Ray and Carter, 2003]. SG block is recommended as a treatment of Ménière's disease [Warrick, 1969]. Sympathetic activity was increased by vertigo attacks in the patients with Ménière's disease [Kawasaki, 1993]. Currently, the sympathetic nervous system in vestibular pathology like Ménière's disease and all vestibular causes of vertigo are studied in humans. Activation of the sympathetic nervous system may adversely affect Eustachian tube function [Franz and Anderson, 2007]. A significantly asymmetric sympathetic hypofunction in the area of the postauricular region of the involved ear in Ménière's disease patients [Yildiz et al., 2007]. SG block can be beneficial in controlling Ménière's disease symptoms, highlighting the influence of the autonomic nervous system. Kim et al. [2017] reported that adrenergic stimulation regulated inner ear fluid ion homeostasis and impairment of this response by β 1- and β 2-ARs in the human endolymphatic sac could be a pathological mechanism underpinning Ménière's disease.

Sudden Deafness

A functional role of sympathetic projections from the SG in CBF regulation could be found in guinea pig [Laurikainen et al., 1993]. In addition, idiopathic sudden sensorineural hearing loss patients showed an altered autonomic regulation [Schulz et al., 2014]. A SG block based on the goal of improving internal ear circulatory disturbance appears to be beneficial for the treatment of sudden hearing loss [Takinami, 2012]. Therefore, oxygen inhalation with drug therapy and SG block is a useful treatment for sudden hearing loss [Li et al., 1991]. It is a safe and effective administration of SG catheter retention with interrupted ropivacaine block [Gao et al., 2015]. However, it is premature to claim that SGB treatment shows a significant efficacy, reevaluation with a larger number of patients is still warranted in the future.

Noise-Induced Hearing Loss

Extensive research has been conducted on the relationship between CBF and the effects of noise exposure on the cochlea [Hawkins, 1971; Hultcrantz et al., 1979; Axelsson et al., 1981; Thorne and Nuttall, 1987; Ryan et al., 1988]. Noise-induced vascular ischemia was demonstrated to lead to reduced auditory sensitivity [Quirk and Seidman, 1995]. Cochlear oxygenation is an efficient way to protect the cochlea from noise-induced damage. Angiotensin receptor antagonist application protects against noise-induced microcirculatory ischemia and auditory sensitivity [Kellerhals, 1972; Miller et al., 1983; Hatch et al., 1991; Goldwyn et al., 1998]. Furthermore, SG blockade im-

proved auditory parameters in rats with normal CBF, suggesting that SG blockade is a potential treatment option for vascular pathologies of the cochlea [Firat et al., 2008].

The discussion on the roles of sympathetic modulation of the cochlea extends to the effects of sympathetic regulation of the cochlear and noise overstimulation. A strong correlation between noise intensity and vagal-sympathetic balance has been reported [Valenti et al., 2012]. Furthermore, a protective role, which becomes significant 1 week after noise overstimulation, has been observed in simultaneous sympathetic nervous system stimulation when the cochlea is overstimulated with the stimuli between 110 and 115 sound pressure level for 10 min [Wada et al., 1999]. Hildesheimer et al. [1991] verified the protective value of cervical sympathectomy in stressful sound exposure conditions which produced a temporary threshold shift (TTS). Horner et al. [2001] used an animal model involving unilateral ablation of the superior cervical ganglion and observed a bilateral protective effect that suggested an intimate relationship between the sympathetic and olivocochlear efferent systems; this highlights new pathways underpinning protective mechanisms against TTS in the cochlea. Giraudet et al. [2002] proposed that protection from TTS under sedation/anesthesia may be due to diminished sympathetic influence. Additionally, a protective role of sympathectomy at different sound exposure levels resulted in a permanent threshold shift [Hildesheimer et al., 2002].

Sympathetic fibers modulate susceptibility to acoustic exposure, but the effects remain controversial [Bielefeld and Henderson, 2007]. Indeed, contradictory results have been reported [Maison et al., 2010]. In a *Dbh*^{-/-} mice model, mutant mice lacking measurable adrenaline or NE were more susceptible than controls to noise exposure. Activity in autonomic motor pathways is regulated by various sensory inputs, including auditory stimuli [Gibbins, 2013]. “Wideband” theta frequency binaural beats postexercise increased sympathetic withdrawal [McConnell et al., 2014]. The response of sympathetic nerves to task demands is mediated by the threat of social assessment, as reported in preliminary studies. However, in a listening task, the relative effects of motivation and emotional stress on physiological responses need to be further studied [Mackersie and Kearney, 2017]. NE in the inner ear is a potential biomarker for acute noise stress in the hippocampus [Jin et al., 2017]. Compared to individuals who did not feel excessive reactions, those who frequently felt excessive reactions to auditory stimuli tended to have excessive sympathetic responses to repeated extensive noises [Kato et al., 2014].

Conclusion

This review article summarizes the recent progress in regulation of the sympathetic nervous system on auditory function. In the peripheral auditory system, the sympathetic nervous system regulates CBF, modulates cochlear efferent fibers, affects hair cells, and influences the habenula region. ARs modulate CBF, and their distribution and function in the cochlea vary. In central auditory pathways, NE is essential for plasticity in the auditory cortex and affects auditory cortex activity. In pathological states, the sympathetic nervous system is associated with noise-induced hearing loss by regulating CBF. ARs may also regulate inner ear fluid ions in several diseases, such as vertigo. Several limitations in the literature exist. The distribution of sympathetic fiber terminals in hair cell regions remains clear, and their regulation of sensory cells has not been demonstrated. The mechanisms and pathways of sympathetic nervous system modulation of auditory function both peripherally and centrally have not been fully defined. The neurobiology of auditory circuit modulation is an area worthy of investigation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Chaoyong Tian drafted the first version of the manuscript. Chaoyong Tian and Dingjun Zha conceived, designed, and wrote jointly the final version of the manuscript. Both authors approved the final version of the manuscript.

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