



## Pathophysiology of tinnitus

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Tinnitus and auditory hallucinations are sensations of hearing in the absence of external sounds. Three main types can be identified: (1) objective tinnitus, which is caused by sounds generated somewhere in the body; (2) subjective tinnitus, which is the perception of meaningless sounds without any physical sound being present; and (3) auditory hallucinations, which are perceptions of meaningful sounds, such as music or speech. The latter two types are phantom sensations [1,2].

Objective tinnitus is rare and is caused by a sound in the body, such as turbulent flow of blood or muscle contractions in the head. Such tinnitus can be heard by an observer in contrast to subjective tinnitus and auditory hallucinations, which can only be heard by the individual who has the tinnitus.

Subjective tinnitus is the most prevalent type of tinnitus and this article is mainly devoted to subjective tinnitus. Subjective tinnitus has many forms. It can be a benign sound that is heard only occasionally or it can be devastating roars that occur 24 hours a day accompanied by hyperacusis and the distortion of sounds, which prevent its sufferers from sleep or the ability to do intellectual work. All degrees of subjective tinnitus occur in between these extremes. Severe tinnitus is also often associated with other symptoms, such as hyperacusis and distortion of sounds. Affective disorders, such as phonophobia and depression, often accompany severe tinnitus and that form of tinnitus can lead to suicide.

With such differences in attributes it is not reasonable to expect that a single cause or a single pathophysiology can be responsible for the symptoms of all forms of severe tinnitus. Instead, many studies have indicated that different forms of tinnitus have different pathophysiology. Subjective tinnitus has many similarities with pain, which also has many different forms and degrees of severity.

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Tinnitus often occurs as a result of insults to the ear, such as from noise exposure or from administration of specific pharmacologic agents, and these factors are taken as the cause of tinnitus. The cause of subjective tinnitus, however, is more often unknown. Subjective tinnitus is one of the three symptoms that constitute Meniere's disease, the cause of which also is unknown. The first objective in finding the cause of tinnitus should be to determine the anatomic location of the abnormality that causes these symptoms. Another important objective in studies of tinnitus is to determine properties of the abnormalities that cause the abnormal neural activity that result in tinnitus and other symptoms that may accompany severe tinnitus. The third objective is to determine how these changes in function have developed. Objective signs of tinnitus are most often absent, however, similar to many forms of pain, and the diagnosis of tinnitus often has to be made solely from the information that the patient provides.

Auditory hallucinations are rare and may be caused by temporal lobe tumors; drugs of various kinds; and psychiatric disorders, such as schizophrenia.

This article discusses where and how tinnitus is generated and what causes the pathologic changes that generate the neural activity that is interpreted as tinnitus. To understand the pathophysiology of tinnitus, tinnitus is compared with other disorders that have similarities with tinnitus, especially central neuropathic pain. Because much more is known about pain than about tinnitus, it is valuable to take advantage of the knowledge about pain in efforts to understand the pathophysiology of tinnitus.

### **Objective tinnitus**

Objective tinnitus involves perception of the sound that is generated in the body and conducted to the cochlea by bone conduction or by sound that is conducted to the middle ear cavity. Sounds that reach the middle ear cavity set the tympanic membrane into vibrations in a similar way as natural sounds, and reach the cochlea by the ossicular chain. Objective tinnitus is not a result of abnormal function of the auditory system; rather, it is caused by a physical sound that is generated in the body and sensed in the same way as normal sounds. Objective tinnitus can usually also be heard by an observer when proper auscultation techniques are used. Objective tinnitus can be caused by blood vessels that are located in the region of the ear. Such tinnitus is pulsatile with the heart rate and it can be caused by constricted vessels where the flow becomes so fast that it becomes turbulent. Arteriovenous malformations, glomus tumors, or aneurysms are examples of vascular malfunctions that can cause pulsatile tinnitus. Temporomandibular joint disorders may cause objective tinnitus in the form of clicking sounds, which also can occur as a result of spontaneous contractions of middle ear muscles or from palatal myoclonus [3]. Sounds, such as breathing

sounds, can be transmitted to the middle ear cavity by a patulous eustachian tube and cause tinnitus because sounds from the nasopharynx reach the middle ear cavity. Objective tinnitus is not discussed further in this article (for details about objective tinnitus, see [3,4]).

### **Subjective tinnitus**

Subjective tinnitus is a perception of sound in the absence of any physical sound. The only evaluation of the nature and the strength of subjective tinnitus that the physician can get is what the patient reports. Although most instances of tinnitus are associated with hearing loss, tinnitus can occur with normal hearing. Subjective tinnitus is a phantom sensation [1] that is caused by pathologies of the ear or the auditory nervous system. In that way, tinnitus is similar to other phantom sensations, such as those that occur after amputation of a limb, where sensations may be referred to different parts of the amputated limb [5].

Subjective tinnitus has many similarities with the symptoms of neurologic disorders, such as paresthesia of the somatosensory system, and in particular with central neuropathic pain [6]. Similar phantom sensations as tinnitus and paresthesia of the somatosensory system rarely occur in other sensory systems but have been reported in vision (phosphene) and olfaction (phantosmia or olfactory hallucinations). Little is known about phantom taste sensations.

#### *Where is subjective tinnitus generated?*

Because the main symptom of tinnitus is a sound, it is natural to expect that the symptoms originate in the ear. Although some forms of tinnitus are most likely generated in the ear by abnormal activity of hair cells or by abnormal functions of the most peripheral part of the auditory nerve, the anatomic location of the physiologic abnormality that causes most forms of severe subjective tinnitus is the central nervous system (CNS) (including the central portion of the auditory nerve). The fact that deaf people can have tinnitus and in particular individuals in whom the auditory nerve has been severed can have tinnitus supports the hypothesis that tinnitus is not always generated (directly) in the ear.

#### *The ear*

Tinnitus is one of the three symptoms of Meniere's disease and because the two other symptoms of that disorder (fluctuating hearing loss and vertigo) are closely related to the function of the ear, it may be assumed that the tinnitus in Meniere's disease is caused by malfunction of structures in the ear. The fact that some forms of tinnitus can be alleviated by section of the auditory nerve [7,8] also indicates that abnormalities in the ear can be the direct cause of tinnitus. As Pulec [7,8] has emphasized, however, the

auditory nerve must be sectioned central to the spiral ganglion to relieve tinnitus, and that indicates that the cause of the tinnitus may be the auditory nerve rather than the ear in such cases.

Electrical current that is passed through the cochlea can reduce the tinnitus in some patients [9,10], which indicates that these forms of tinnitus are generated in the ear. Electrical current passed through the cochlea changes the activity in auditory nerve fibers. If tinnitus is caused by deprivation of neural activity in the auditory nerve, electrical current may restore activity. The finding that cochlear implants can alleviate tinnitus in some patients [11,12] supports that hypothesis.

Exposure to loud sounds (noise) or administration of ototoxic drugs can cause tinnitus that is associated with hearing loss. Noise and ototoxic drugs are assumed primarily to affect the ear (hair cells) but the tinnitus may in fact be generated in the CNS as a result of deprivation of input or perhaps because of abnormal input from the ear. To complicate matters further, there is increasing evidence that hearing loss from noise exposure is not solely affecting hair cells but overexposure to sound is also associated with CNS changes that can be detected morphologically [13] and physiologically [14–17]. Even presbycusis may have central components [18]. The physiologic changes that cause tinnitus may occur because of deprivation of input that may change the function of CNS structures as a result of expression of neural plasticity.

Tinnitus only occurs in some individuals with hair cell injuries and that indicates that factors other than injuries to hair cells are necessary for the development of tinnitus. If deprivation of input to the CNS from the ear always caused tinnitus, then one would expect that auditory nerve section would cause tinnitus. That is obviously not the case because auditory nerve section has been used successfully to treat some forms of tinnitus [8]. This again emphasizes the complexity of tinnitus and the fact that such disorders as tinnitus often require the involvement of more than one factor to develop symptoms. Although little is known about the primary factors that cause tinnitus, nothing is known about these additional factors that seem to be necessary for development of tinnitus.

That means that whereas the primary cause of the tinnitus may be malfunction of the ear, the anatomic location of the structures that generate the abnormal neural activity that is perceived as sound may not be located in the ear at all, but rather somewhere in the CNS. The spontaneous discharge rate of auditory nerve fibers in animals that have been treated in ways that cause tinnitus in humans (ie. by ototoxic antibiotics) is not elevated but rather reduced [19–21], as is also the case in animals with acute injury to the cochlea [22]. This indicates that tinnitus may not be directly related to the spontaneous discharge rate of auditory nerve fibers, which seems surprising because tinnitus is regarded as a hyperactive disorder. Administration of salicylate can cause an increase in the spontaneous discharge rates of single auditory nerve fibers [1,23,24] in experimental animals. And yet, salicylates are used to treat tinnitus in some patients.

These observations support the hypothesis that subjective tinnitus is not related to the discharge rate of auditory nerve fibers.

Injury to the ear may act to cause tinnitus by deprivation of input to the auditory nervous system. Many studies of other systems have shown that deprivation of input to CNS structures can cause hyperactivity of specific structures through expression of neural plasticity. Properties other than the discharge rate may be correlated better to tinnitus. It has been suggested that phase-locking of the activity in many nerve fibers may be a factor more closely related to tinnitus than the discharge rate [25,26].

#### *The nervous system*

An increasing number of studies have shown that most forms of severe tinnitus are caused by abnormal functioning of the nervous system. The expression of neural plasticity plays an important role in the development of such tinnitus and the symptoms and signs that often accompany severe tinnitus, such as hyperacusis, and affective disorders, such as phonophobia and depression.

The tinnitus and other symptoms that often accompany tinnitus, such as hyperacusis, phonophobia, and depression may be caused by changes in the function of the auditory nervous system that normally responds to sounds or it may be caused by an abnormal involvement of parts of the nervous system that are normally not involved in processing sounds. Several studies have indicated that tinnitus and the other signs that often accompany severe tinnitus (hyperacusis and phonophobia) may be caused by changes in the function of nuclei in the ascending auditory pathways [15,27] or by redirection of information to regions of the CNS that normally do not receive that kind of auditory input [28–30]. Indications that the nonclassical auditory pathways may be involved in tinnitus have been shown in some studies that showed that tinnitus in some individuals was affected by electrical stimulation of the somatosensory system [29]. Because the classical ascending auditory pathways have no known input from the somatosensory system it was concluded that this cross-modulation was a result of involvement of the nonclassical auditory pathway. Other studies have shown other evidence that some individuals with tinnitus have abnormal cross-modal interactions, especially with the somatosensory system [31,32], which supports the hypothesis that tinnitus is generated at anatomically different locations in the CNS than those that normally process sounds. Earlier studies have shown evidence that electrical stimulation of the skin behind the ears can relieve tinnitus [33] and stimulation of the skin of the fingers can also relieve tinnitus in some individuals [34,35]. Such cross-modal interaction is assumed to involve the nonclassical auditory pathways [29] because that system receives input from other sensory systems, unlike the classical system.

The fact that temporomandibular joint disorders often are associated with tinnitus [36] and that the tinnitus is often alleviated when the temporomandibular joint is treated [37] may be explained by interaction between

the somatosensory system (the sensory trigeminal nerve) and the auditory system [38].

#### *The nonclassical auditory system*

The nonclassical pathways (also known as the *extralemniscal pathways* or the *nonspecific, diffuse and polysensory pathways* [39–45]) ascend in parallel to the much better known classical pathways [41,44,45]. The nonclassical pathways receive their main auditory input from the central nucleus of the inferior colliculus, which belongs to the classical ascending pathways.

Little is known about the normal function of the nonclassical pathways but studies have found indications that these pathways are active in some patients with severe tinnitus. Recent studies have shown evidence that the nonclassical auditory pathways are active in loudness perception in young children [46] but rarely in individuals above the age of 20 years [29,46].

The nonclassical pathways use the dorsal and medial thalamic nuclei (medial geniculate body [MGB], dMGB and mMGB) as their relay nuclei, whereas the classical auditory pathways use the ventral thalamic nucleus (vMGB) [45]. The thalamic nuclei of the nonclassical auditory pathways project to association cortices and nonsensory structures, such as those of the limbic system, whereas the thalamic nuclei of the classical pathways project to the primary auditory cortex. The nonclassical auditory pathways have subcortical connections to limbic structures, whereas the classical auditory pathways connect to limbic structures through a long chain of neurons where the information is processed and modulated by intrinsic and extrinsic neural activity. The nuclei of the nonclassical pathways perform less specific analysis of sounds than those of the classical pathways [40,45, 47]. Another difference between the two pathways is that the nonclassical auditory pathways receive input not only from the ear but also from sensory organs of other sensory modalities. The best known are from the somatosensory system and the vision. The fact that neurons in the nuclei of the nonclassical auditory system receive input from the somatosensory system has been used in studies of the involvement of the nonclassical auditory system in perception of loudness [29,46].

#### *Involvement of nonauditory parts of the CNS*

The mMGB and dMGB project directly to the lateral nucleus of the amygdala (Fig. 1) [45,48], and this may explain the affective components that often accompany severe tinnitus (and chronic pain). The findings that limbic structures are more active in response to sound stimulation in some patients with tinnitus [28] support the findings that the nonclassical auditory system is involved in tinnitus.

#### *How is tinnitus generated?*

The cause of tinnitus is unknown in most cases. Tinnitus may occur together with changes in the cochlea or the CNS. Such changes may be

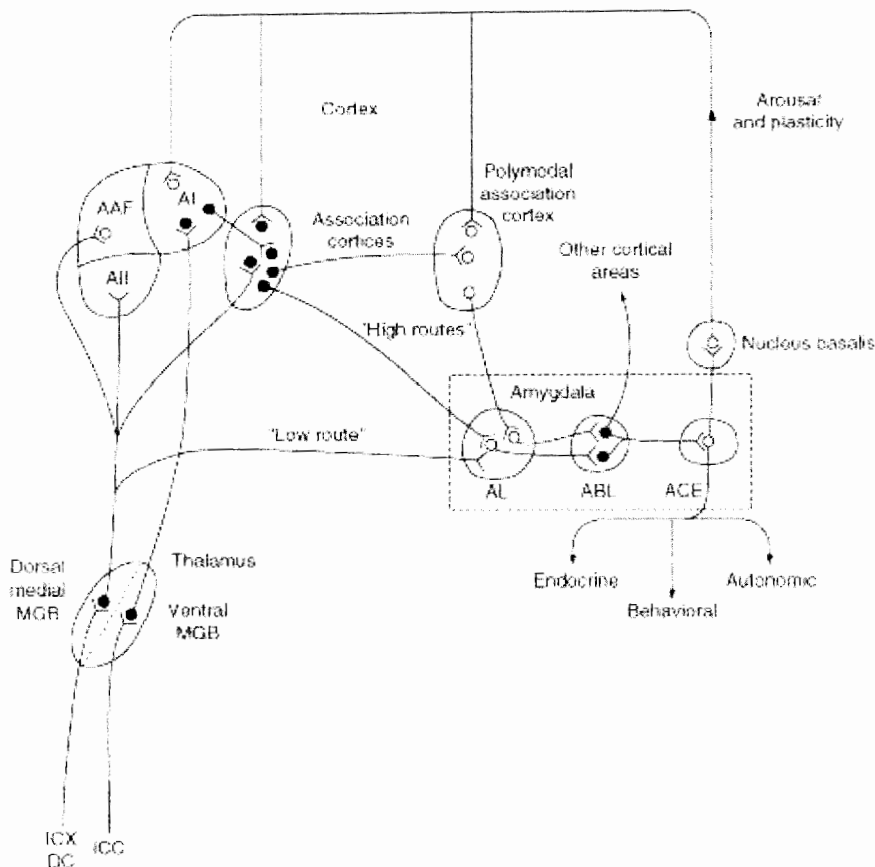


Fig. 1. Schematic diagram showing connections from the classical and the nonclassical ascending auditory pathways to the nuclei of the amygdala. Some connections from the amygdala nuclei are also shown. AAF— anterior auditory field; ABL= basolateral nucleus of the amygdala; ACE= central nucleus of the amygdala; AI= primary auditory cortex; AII= secondary auditory cortex; AL= lateral nucleus of the amygdala; DC= dorsal cortex of the inferior colliculus; ICC= central nucleus of the inferior colliculus; ICX= external nucleus of the inferior colliculus; MGB= medial geniculate body. (From Møller AR. Sensory systems: anatomy and physiology. San Diego: Academic Press; 2002; with permission.)

morphologic in nature and can be observed using histologic methods. An example of morphologic changes that are often accompanied by tinnitus is injuries to cochlear hair cells, caused for example by exposure to loud noise, especially impulsive noise. Tinnitus does not occur in all instances of noise-induced hearing loss, however, and the severity of the tinnitus is not directly related to the degree of hearing loss. There is doubt that tinnitus is caused directly by morphologic changes in the cochlea. It seems more likely that most forms of tinnitus that are related to pathologies in the ear and the auditory nerve are caused by abnormal input to CNS structures in the form

of deprivation of auditory input or generation of novel input. Deprivation of input may cause expression of neural plasticity that can take the form of tinnitus and other symptoms. Similarly, injuries to the auditory nerve, such as those from vestibular schwannomas, or irritation of the auditory nerve from close contact with a blood vessel may generate abnormal neural activity that can also cause changes in the function of central structures. This means that most forms of severe tinnitus are probably caused by a sequence of complex events.

Salicylates and diuretics (furosemide or ethacrynic acid) may cause tinnitus as can many other drugs, such as quinine, indomethacin, aminoglycoside antibiotics, and cisplatin [49,50]. How this may occur is unknown.

Tinnitus almost always accompanies vestibular schwannomas but tinnitus from vestibular schwannomas represents only a small fraction of the patients who have severe tinnitus. Tinnitus almost always is the first symptom of a vestibular schwannoma and the tinnitus may be worse after removal of a vestibular schwannoma [51]. Although this may indicate that structural injuries can cause tinnitus, the neural activity that causes the tinnitus may not be generated in the auditory nerve itself but rather in more central structures. The changes in the central structures may be caused by novel input from the injured auditory nerve or reduced input. That hypothesis is supported by the observation that auditory nerve section does not relieve tinnitus in all such patients.

Other forms of surgical manipulation of the auditory nerve such as may occur during microvascular decompression of nearby cranial nerves (CN VII and CN V), may also cause tinnitus. Vascular contact with the intracranial portion of the auditory nerve (microvascular compression) has been associated with tinnitus because the tinnitus may disappear when the offending vessel is moved off the auditory nerve [52–54]. Vascular compression of cranial nerves [54] has been regarded to cause such symptoms as hemifacial spasm (HFS), trigeminal neuralgia (TGN), disabling positional vertigo (DPV), and tinnitus [53,55] because of injuries to the respective cranial nerves. Evidence from studies of HFS [25,56], however, seems to indicate that the effect is instead an irritation that causes abnormal neural activity that in turn changes the function of more central structures through processes known as the *kindling phenomenon* [57] or *neural plasticity* [58]. Vascular compression may occur without any symptoms [59] indicating that other factors are necessary for the development of tinnitus than vascular contact with the auditory nerve [56]. The outcome of MVD operations for tinnitus is much more favorable in women than in men [53], yet more evidence that supports the hypothesis that several factors are involved in causing tinnitus. These additional factors that are necessary for expression of symptoms are essentially unknown but slight differences in resting membrane potentials in neurons in the auditory nervous system, or abnormal synaptic threshold or efficacy, may be factors that are important for the development of such disorders. These factors may not produce any

noticeable symptoms or signs and only when occurring together with such factors as vascular compression do they manifest. Disorders that can be cured by MVD operations, and many other disorders, depend on the presence of several factors being present together for the development of symptoms and for maintaining these symptoms [56,60].

That patients with tinnitus may have different etiology is supported by the finding that patients with unilateral tinnitus have much better results of MVD operations than patients with bilateral tinnitus [61]. This again emphasizes the complexity of subjective tinnitus.

Many forms of subjective tinnitus become less treatable by MVD with the duration of the symptoms [53] indicating that the changes in the function of the CNS that cause the tinnitus become more established with time and more difficult to reverse. Similar observations have been made in other disorders that can be treated by MVD, such as TGN [62]. Also, neuropathic pain becomes more difficult to treat with time.

#### *The role of neural plasticity in tinnitus*

Expression of neural plasticity occurs in all parts of the CNS and it can be caused by many different factors, where deprivation of input, abnormal input, or injury are the most common. In fact, it is assumed that the role of neural plasticity is to shift functions of injured structures to other parts of the CNS. This is what is termed *good plasticity* [45]. There is also bad plasticity, which causes symptoms and signs of diseases [60]. Bad plasticity often causes hypersensitivity and hyperactivity and may redirect information to other parts of the CNS by unmasking dormant synapses [45,63] or by creating new connections by axonal sprouting.

Many studies have supported the hypothesis that neural plasticity plays an important role in some forms of tinnitus [29,30,60,64–66]. Deprivation of input can activate neural plasticity, which can cause changes in synaptic function [63,67,68], a form of learning. Functional changes induced by neural plasticity can be transient, persistent, or permanent, but most functional changes are reversible by suitable stimulation. Most of the understanding of the role of neural plasticity in causing symptoms and signs of disorders [60] comes from studies of neuropathic pain [69–71].

Animal experiments have shown evidence that deprivation of input caused by hearing loss can cause nuclei of the auditory pathways to show signs of hypersensitivity [15] and similar hyperactivity has been linked to severe tinnitus. Exposure to loud sounds can cause persistent hyperactivity in nuclei of the auditory system [27,72]. Hyperactivity and changed temporal integration often occur in parallel as signs of functional changes, such as those induced through the expression of neural plasticity. Abnormal temporal integration has been shown in animal experiments to occur in the auditory system after overstimulation [27,72] and from deprivation of input [16] and in humans after injuries to the auditory nerve [73].

When synapses that are normally not conducting nerve impulses become conducting (unmasking of dormant synapses [63,68]), it can cause redirection of information. It has been hypothesized that such rewiring may be responsible not only for tinnitus, but also for the symptoms that often accompany severe tinnitus, such as hyperacusis, and affective disorders, such as phonophobia and depression, because auditory information is redirected to portions of the CNS that normally do not receive auditory information, at least not in that form. It should be possible to reverse functional changes in the auditory nervous system that are caused by expression of neural plasticity by appropriate sound stimulation and a method that makes use of that, tinnitus retraining therapy, is currently in use for treatment of tinnitus [74]. Future investigations will no doubt further develop such treatments.

Evidence has been presented that symptoms of several other diseases can also be caused by expression of neural plasticity [60], such as hemifacial spasm [56], synkinesis after facial nerve injuries [75], and in particular central neuropathic pain [30,45,76]. A recent finding has demonstrated that exposure to rapid pressure changes can alleviate the symptoms of Meniere's disease including tinnitus [77]. A pulsating pressure applied to the middle ear cavity (through a plastic tube inserted in the tympanic membrane) alleviated symptoms of Meniere's disease. This stimulation of the vestibular apparatus by the pulsating air pressure may have caused an expression of neural plasticity, which indicates that neural plasticity is involved in generating the symptoms of Meniere's disease.

#### *Similarities between pain and tinnitus*

Some forms of pain have similarities with severe tinnitus [6,30,78]. Shea et al [79] discussed similarities between tinnitus and pain in connection with the use of lidocaine or lidocaine-like drugs in treatment of tinnitus. Lidocaine, administered intravenously, is one of a few drugs that can effectively alleviate tinnitus, but attempts to find drugs with the same beneficial effect on tinnitus that can be administered orally has been disappointing. Lidocaine works from the inside of cells and blocks sodium channels after it has been protonated. Tonndorf [78] discussed the similarities between tinnitus and pain related to the gating theory of Melzack and Wall [80]. Møller [6,30] discussed the similarities between severe tinnitus and central neuropathic pain. Considering that much more is known about the pathophysiology of pain than of tinnitus, it is valuable to consider hypotheses and results of studies of pain for the understanding of the pathophysiology of tinnitus. Some forms of tinnitus [1,81] and some forms of pain are phantom sensations that are difficult to describe quantitatively by patients.

The perception of sensory stimuli including pain is abnormal in many individuals with severe pain and individuals with tinnitus often have abnormal perception of sounds (hyperacusis). Both pain and tinnitus are often accompanied by affective symptoms, such as depression. Some signs, such as abnormal temporal integration of painful stimuli in individuals with

severe neuropathic pain of central origin [82], are similar to what has been observed in animal experiments after deprivation of auditory input [16] or after overstimulation with sound [27,72].

Like tinnitus, some forms of pain (central neuropathic pain) are caused by expression of neural plasticity and neural plasticity has been studied extensively in this regard [60,70,83–85]. Some forms of pain can be reversed by appropriate sensory stimulation (transdermal electrical nerve stimulation) [86], supporting the hypothesis that this kind of pain is caused by reversible changes in synaptic efficacy. Tinnitus can often be alleviated by appropriate sound stimulation (tinnitus retraining therapy [74]).

The neural circuits in the dorsal horn of the spinal cord are of special interest in regard to pain and the function of these circuits has been studied extensively. There are similarities between the transformation of dorsal horn neurons (especially the wide dynamic range neurons) that cause central neuropathic pain and the changes that occur in the nuclei of the ascending auditory pathways in animals after treatments that normally cause tinnitus in humans.

The neurons in the dorsal horn of the spinal cord normally process innocuous and noxious cutaneous stimuli and input from proprioceptors. The processing that normally occurs in those circuits and in different forms of pain has been divided into four main states [70]. The first state is the normal state, where innocuous and noxious stimulations are processed separately and transmitted to more central regions. In the second state the sensitivity to sensory stimulation is reduced. In the auditory system, that corresponds to hearing loss. In the third state, transient sensitization of the dorsal horn neurons occurs and the sensibility to noxious stimulation is increased. Normally innocuous stimulation causes pain (allodynia) and exaggerated reaction to painful stimulations (hyperalgesia). This situation, which occurs after injuries and from acute inflammation, is known as *neuropathic pain* and it resembles the changes that occur in the auditory system immediately after strong sound exposure. (The term *neuropathic pain* means pain caused by the nervous system. Neurologists usually reserve the term for pain related to peripheral nerves and cranial nerves.)

The third mode of processing in the dorsal horn is explained by facilitated synaptic transmission, caused by increased excitation and decreased inhibition [70]. This is caused by expression of neural plasticity [85] involving the wide dynamic range neurons [70,87,88], which receive input from several types of mechanoreceptors and pain receptors in the skin. It is assumed that these changes are caused by expression of neural plasticity and that they cause the symptoms and signs of persistent central neuropathic pain.

In the fourth state of processing in the dorsal horn, the neural circuits are reorganized. This state, known as *central neuropathic pain*, is persistent and includes allodynia and hyperalgesia. The reorganization of the CNS structures consists of changes in synaptic efficacy or establishment of new connections by sprouting of axons or severing of connections. This state has

similarities to the third state but it is persistent. The degeneration of nerve fibers, such as from tissue injury [69], can cause vacant synaptic sites that may be invaded by sprouting of other kinds of fibers [70].

The increased sensitivity to sounds (hyperacusis) that is often experienced by individuals with severe tinnitus corresponds to hyperalgesia. It has similarities to the symptoms of pain that are experienced in the third and fourth states of changes in the processing in the dorsal horn. The fact that some normal sounds are perceived as being painful corresponds to allodynia.

There is evidence that neurons in the inferior colliculus and perhaps the cochlear nucleus may undergo similar changes in function as the wide dynamic range neurons. Such changes could cause tinnitus and redirection of information to the nonclassical auditory pathways.

#### *Redirection of information and the role of the nonclassical auditory pathways*

Changes in synaptic efficacy can open connections in the CNS that are normally not conducting and that can redirect information in the CNS; thereby auditory information may reach parts of the CNS that normally do not receive auditory information. The auditory information could be channeled to specific structures through other than normal pathways. Auditory information may activate the nonclassical auditory pathways in some individuals with severe tinnitus [29,31,32,65,89] and such redirection can explain some of the other symptoms that are often associated with tinnitus, such as affective disorders [29]. Involvement of the nonclassical pathways may also explain the abnormal perception of sounds, such as hyperacusis and distortion of sounds, which often accompanies severe tinnitus. Many studies have shown that tinnitus is matched to sounds with very low intensity and that tinnitus is difficult to mask [90–92]. These differences may be explained by the hypothesis that the physiologic abnormality that generates tinnitus is not the ear or that the neural activity that generates the sensation of tinnitus is different from that normally evoked by sound. This abnormal neural code may be generated in neural circuits other than those that normally process sounds, indicating that redirection of information has occurred.

#### *Implications of involvement of the nonclassical auditory pathways*

The classical and the nonclassical ascending auditory pathways differ in several ways. The classical pathway projects to primary auditory cortices by nuclei in the vMGB of the thalamus [41,44,45], whereas the nonclassical or extralemniscal pathways uses the dMGB and mMGB of the thalamus and projects to secondary and association cortices bypassing the primary auditory cortices [40,44,45]. The dorsal and medial thalamic nuclei also have a direct projection to the lateral nucleus of the amygdala (see Fig. 1). Much less is known about the nonclassical pathways than the classical pathways.

both anatomically and physiologically. Neurons in the nuclei of the classical pathways respond with sharp frequency tuning and have specific responses to many different kinds of sounds [44,45], whereas neurons in the nonclassical pathways respond less specific to sound [40,47,93]. Although neurons in the classical auditory pathways only respond to sound, some neurons in the nonclassical pathways also respond to other sensory modalities, such as somatosensory [40,94,95] and visual stimuli. Recently, several anatomic studies have demonstrated connections between the somatosensory system and the auditory system, both from the body (dorsal column nuclei) [96] and the head (trigeminal nucleus) [38,96].

Little is known about the normal function of the nonclassical pathways but recent studies have indicated that the nonclassical pathways in children are involved in loudness perception. That involvement decreases gradually with age [46] and involvement of the nonclassical pathways is rare in individuals above the age of 20 years [29,46]. There is increasing evidence that the nonclassical pathways may be activated in individuals with some forms of tinnitus [29,31,65].

The different processing that occurs in the nuclei of the nonclassical pathways [47,93,97] may explain why some individuals with tinnitus perceive sounds differently. It may explain hyperacusis and the fact that tinnitus is difficult to mask with sounds and that matching of tinnitus to physical sounds consistently results in unrealistic low values.

The direct connection from the thalamic nuclei of the nonclassical pathways to the amygdala [44,45] (the low route [48]) may explain the affective components of tinnitus that some patients experience [29], such as fear reactions [98], phonophobia, and depression. The lateral nucleus of the amygdala to which the nonclassical auditory system projects connects to other nuclei of the amygdala, which connect to many other limbic structures and many other parts of the CNS (see Fig. 1) [99,100]. Studies using functional imaging have confirmed abnormal involvement of limbic structures in some patients with tinnitus [28].

Auditory information can also reach limbic structures, such as the amygdala, through the classical auditory system (the high route) [48], but that occurs through a long chain of neurons in the primary auditory cortex, secondary auditory cortex, and association cortices (see Fig. 1) [101]. The information that reaches the amygdala through that route is subjected to extensive processing and modulation by neural activity generated by intrinsic and extrinsic sources. The auditory information that reaches the amygdala through the direct route from the thalamic nuclei of the nonclassical auditory pathway is little processed and the ability to modulate that activity is limited (see Fig. 1) [45].

The nuclei of the amygdala are involved in fear reactions and in affective disorders and abnormal auditory input through the low route may explain the affective components of some forms of tinnitus. The amygdala connects to many parts of the CNS including those controlling endocrine and

autonomic systems (see Fig. 1) and that may explain the abnormal activation of autonomic systems, such as the sympathetic nervous system, that often accompanies severe tinnitus. It is a general observation that the tinnitus is often affected by stress and it is known that the sympathetic nerve system can modulate the sensitivity of sensory receptors in other sensory systems, such as the somatosensory system [45]. It is possible that the adrenergic innervation of the cochlea may not only affect the blood flow but may also affect the sensitivity of hair cells because these autonomic nerves terminate close to the hair cells [102]. The norepinephrine that is secreted from these adrenergic nerve fibers may cause hair cells to become activated without any sound being present. The finding that sympathectomy can alleviate tinnitus in some patients [103,104] supports the hypothesis that the sympathetic nervous system is involved in some forms of tinnitus.

### **Auditory hallucinations**

Auditory hallucinations are generated in cortical structures of the nervous system. Temporal lobe tumors must be ruled out in a person who presents with auditory hallucinations, although that is a rare cause. Such hallucinations may include hearing music or voices. Auditory hallucinations often occur in psychiatric disorders, such as schizophrenia, but can also occur postoperatively particularly if ketamine-like drugs have been used. Various street drugs also cause auditory hallucinations, often in the form of hearing voices.

### **References**

- [1] Jastreboff PJ. Phantom auditory perception (tinnitus): mechanisms of generation and perception. *Neurosci Res* 1990;8:221–54.
- [2] Jastreboff PJ. Tinnitus as a phantom perception: theories and clinical implications. In: Vernon JA, Møller AR, editors. *Mechanisms of tinnitus*. Boston: Allyn & Bacon; 1995. p. 73–93.
- [3] Schleuning AJ. Management of the patient with tinnitus. *Med Clin North Am* 1991; 75:1225–37.
- [4] Andersen RG, Meyerhoff WL. Otolologic pathology and tinnitus. In: Clark JG, Yanick P, editors. *Tinnitus and its management*. Springfield, IL: Charles C Thomas Publishers; 1984.
- [5] Melzack R. Phantom limbs. *Sci Am* 1992;266:120–6.
- [6] Møller AR. Similarities between chronic pain and tinnitus. *Am J Otol* 1997;18:577–85.
- [7] Pulec JL. Tinnitus: surgical therapy. *Am J Otol* 1984;5:479–80.
- [8] Pulec JL. Cochlear nerve section for intractable tinnitus. *Ear Nose Throat J* 1995;74: 469–76.
- [9] Cazals Y, Negrevergne M, Aran JM. Electrical stimulation of the cochlea in man: hearing induction and tinnitus suppression. *J Am Audiol Soc* 1978;3:209–13.
- [10] Aran JM, Cazals I. Electrical suppression of tinnitus. *Ciba Foundation Symposium* 85. London: Pitman Books; 1981.

- [11] Sininger YS, Mobley JP, House W, Nielsen DW. Intra-cochlear electrical stimulation for tinnitus suppression in a patient with near-normal hearing. In: Feldmann H, editor. Proceedings of the III International Tinnitus Seminar. Karlsruhe, West Germany: Harsch Verlag; 1987.
- [12] McKerrow WS, et al. Tinnitus suppression by cochlear implants. *Ann Otol Rhinol Laryngol* 1991;100:552–8.
- [13] Morest DK, Ard MD, Yurgelun-Todd D. Degeneration in the central auditory pathways after acoustic deprivation or over-stimulation in the cat. *Anat Rec* 1979;193:750.
- [14] Willott JF, Lu SM. Noise induced hearing loss can alter neural coding and increase excitability in the central nervous system. *Science* 1981;16:1331–2.
- [15] Gerken GM, Saunders SS, Paul RE. Hypersensitivity to electrical stimulation of auditory nuclei follows hearing loss in cats. *Hear Res* 1984;13:249–60.
- [16] Gerken GM, Solecki JM, Boettcher FA. Temporal integration of electrical stimulation of auditory nuclei in normal hearing and hearing-impaired cat. *Hear Res* 1991;53:101–12.
- [17] Szczepaniak WS, Møller AR. Evidence of neuronal plasticity within the inferior colliculus after noise exposure: a study of evoked potentials in the rat. *Electroencephalogr Clin Neurophysiol* 1996;100:158–64.
- [18] Willott JF, Turner JG, Sundin VS. Effects of exposure to an augmented acoustic environment on auditory function in mice: roles of hearing loss and age during treatment. *Hear Res* 2000;142:79–88.
- [19] Salvi RJ. Central components of the temporary threshold shift. In: Henderson D, Hamernik RP, Donsanji DS, Mills JH, editors. Effect of noise on hearing. New York: Raven Press; 1976. p. 247–60.
- [20] Salvi RJ, Ahroon WA. Tinnitus and neural activity. *J Speech Lang Hear Res* 1983;26: 629–32.
- [21] Liberman MC, Kiang NYS. Acoustic trauma in cats. *Acta Otolaryngol Suppl* (Stockh) 1978;358:1–63.
- [22] Evans EF. Temporary sensorineural hearing losses and eighth nerve changes. In: Henderson D, Hamernik RP, Donsanji DS, Mills JH, editors. Effect of noise on hearing. New York: Raven Press; 1976. p. 199–221.
- [23] Evans EF, Wilson JP, Borerwe TA. Animal models of tinnitus. *Ciba Foundation Symposium* 85. London: Pitman Books; 1981.
- [24] Evans EF, Borerwe TA. Ototoxic effects of salicylate on the responses of single cochlear nerve fibers and on cochlear potentials. *Br J Audiol* 1982;16:101–8.
- [25] Møller AR. Pathophysiology of tinnitus. *Ann Otol Rhinol Laryngol* 1984;93:39–44.
- [26] Eggermont JJ. On the pathophysiology of tinnitus: a review and a peripheral model. *Hear Res* 1990;48:111–24.
- [27] Kaltenbach JA. Hyperactivity in the dorsal cochlear nucleus after intense sound exposure and its resemblance to tone-evoked activity: a physiological model for tinnitus. *Hear Res* 2000;140:165–72.
- [28] Lockwood A, Salvi R, Coad M, Towsley M, Wack D, Murphy B. The functional neuroanatomy of tinnitus: evidence for limbic system links and neural plasticity. *Neurology* 1998;50:114–20.
- [29] Møller AR, Møller MB, Yokota M. Some forms of tinnitus may involve the extralemniscal auditory pathway. *Laryngoscope* 1992;102:1165–71.
- [30] Møller AR. Similarities between severe tinnitus and chronic pain. *J Am Acad Audiol* 2000;11:115–24.
- [31] Caeace AT, Cousins JP, Parnes SM, McFarland DJ, Semenov D, Holmes T, et al. Cutaneous-evoked tinnitus. II: Review of neuroanatomical, physiological and functional imaging studies. *Audiol Neurotol* 1999;4:258–68.
- [32] Caeace AT, Cousins JP, Parnes SM, Semenov D, Holmes T, McFarland DJ, et al. Cutaneous-evoked tinnitus. I: Phenomenology, psychophysics and functional imaging. *Audiol Neurotol* 1999;4:247–57.

- [33] Engelberg M, Bauer W. Transcutaneous electrical stimulation for tinnitus. *Laryngoscope* 1985;95:1167–73.
- [34] Kaada B, Hognestad S, Havstad J. Transcutaneous nerve stimulation (TNS) in tinnitus. *Scand Audiol (Stockh)* 1989;18:211–7.
- [35] Rahko T, Kotti V. Tinnitus treatment by transcutaneous nerve stimulation (TNS). *Acta Otolaryngol Suppl (Stockh)* 1997;529:88–9.
- [36] Morgan DH. Tinnitus of TMJ origin. *J Craniomandibular Practice* 1992;10:124–9.
- [37] Morgan DH. Temporomandibular joint surgery: correction of pain, tinnitus, and vertigo. *Dent Radiogr Photogr* 1973;46:27–46.
- [38] Shore SE, Vass Z, Wys NL, Altschuler RA. Trigeminal ganglion innervates the auditory brainstem. *J Comp Neurol* 2000;419:271–85.
- [39] Graybiel AM. Some fiber pathways related to the posterior thalamic region in the cat. *Brain Behav Evol* 1972;6:363–93.
- [40] Aitkin LM. The auditory midbrain, structure and function in the central auditory pathway. Clifton, NJ: Humana Press; 1986.
- [41] Webster DB. An overview of mammalian auditory pathways with an emphasis on humans. In: Webster DB, Popper AN, Fay RR, editors. The mammalian auditory pathway: neuroanatomy. New York: Springer Verlag; 1992. p. 1–22.
- [42] Rouiller EM. Functional organization of the auditory system. In: Ehret G, Rom R, editors. The central auditory system. New York: Oxford University Press; 1997. p. 3–96.
- [43] Kvasnak E, Suta D, Popelar J, Syka J. Neuronal connections in the medial geniculate body of the guinea-pig. *Exp Brain Res* 2000;132:87–102.
- [44] Møller AR. Hearing: its physiology and pathophysiology. San Diego: Academic Press; 2000.
- [45] Møller AR. Sensory systems: anatomy and physiology. San Diego: Academic Press; 2002.
- [46] Møller AR, Rollins P. The non-classical auditory system is active in children but not in adults. *Neurosci Lett* 2002;319:41–4.
- [47] Syka J, Popelar J, Kvasnak E. Response properties of neurons in the central nucleus and external and dorsal cortices of the inferior colliculus in guinea pig. *Exp Brain Res* 2000;133:254–66.
- [48] LeDoux JF. Brain mechanisms of emotion and emotional learning. *Curr Opin Neurobiol* 1992;2:191–7.
- [49] Seligmann H, Podoshin L, Ben-David J, Fradis M. Drug-induced tinnitus and other hearing disorders. *Drug Saf* 1996;14:198–212.
- [50] Simpson JJ, Davies E. Recent advances in the pharmacological treatment of tinnitus. *Trends Pharmacol Sci* 1999;20:12–8.
- [51] House JW, Brackmann DE. Tinnitus: surgical treatment. *Tinnitus (Ciba Foundation Symposium 85)*. London: Pitman Books; 1981.
- [52] Kondo A, Ishikawa J, Yamasaki T, Konishi T. Microvascular decompression of cranial nerves, particularly of the seventh cranial nerve. *Neurol Med Chir (Tokyo)* 1980;20:739–51.
- [53] Møller MB, Møller AR, Jannetta PJ, Jho HD. Vascular decompression surgery for severe tinnitus: selection criteria and results. *Laryngoscope*. 1993;103:421–427.
- [54] Møller AR. Vascular compression of cranial nerves. I: History of the microvascular decompression operation. *Neurol Res* 1998;20:727–31.
- [55] Møller MB, Møller AR, Jannetta PJ, Jho HD, Sekhar L. Microvascular decompression of the eighth nerve in patients with disabling positional vertigo: selection criteria and operative results in 207 patients. *Acta Neurochir (Wien)* 1993;125:75–82.
- [56] Møller AR. Cranial nerve dysfunction syndromes: pathophysiology of microvascular compression. In: Barrow DL, editor. *Neurosurgical topics book 13: surgery of cranial nerves of the posterior fossa*. Park Ridge, IL: American Association of Neurological Surgeons; 1993. p. 105–29.
- [57] Goddard GV. Amygdaloid stimulation and learning in the rat. *J Comp Physiol Psychol* 1964;58:23–30.

- [58] Møller AR. Vascular compression of cranial nerves. II. Pathophysiology. *Neurol Res* 1999;21:439–43.
- [59] Sunderland S. Microvascular relations and anomalies at the base of the brain. *J Neurol Neurosurg Psychiatry* 1948;11:243–57.
- [60] Møller AR. Symptoms and signs caused by neural plasticity. *Neurol Res* 2001;23:565–72.
- [61] Vasama JP. Microvascular decompression of the cochlear nerve in patients with severe tinnitus: preoperative findings and operative outcome in 22 patients. *Neurol Res* 1998; 20:242–8.
- [62] Apfelbaum R. Surgery for tic douloureux. *Clin Neurosurg* 1984;31:357–68.
- [63] Wall PD. The presence of ineffective synapses and circumstances which unmask them. *Philos Trans R Soc Lond B Biol Sci* 1977;278:361–72.
- [64] Møller AR, Møller MB, Jannetta PJ, Jho HD. Compound action potentials recorded from the exposed eighth nerve in patients with intractable tinnitus. *Laryngoscope* 1992;102:187–97.
- [65] Cacace AT, Lovely TJ, McFarland DJ, Parnes SM, Winter DF. Anomalous cross-modal plasticity following posterior fossa surgery: some speculations on gaze-evoked tinnitus. *Hear Res* 1994;81:22–32.
- [66] Cacace AT. Expanding the biological basis of tinnitus: Cross modal origins and the role of neuroplasticity. *Hear Res* 2003;175:112–32.
- [67] Ahissar E, Ahissar M. Plasticity in auditory cortical circuitry. *Curr Opin Neurobiol* 1994; 4:580–7.
- [68] Sandkühler J, Benrath J, Brechtel C, Ryuscheweyh R, Heinke B. Synaptic mechanisms of hyperalgesia. In: Sandkühler J, Bromm B, Gebhart GF, editors. *Nervous system plasticity and chronic pain*. Amsterdam: Elsevier; 2000. p. 81–100.
- [69] Dubner R, Basbaum AI. Spinal dorsal horn plasticity following tissue or nerve injury. In: Wall PD, Melzack R, editors. *Textbook of pain*. 3rd edition. Edinburgh: Churchill Livingstone; 1994. p. 225–41.
- [70] Doubell TP, Mannion RJ, Woolf CJ. The dorsal horn: state-dependent sensory processing, plasticity and the generation of pain. In: Wall PD, Melzack R, editors. *Handbook of pain*. 4th edition. Edinburgh: Churchill Livingstone; 1999. p. 165–81.
- [71] Woolf CJ, Salter MW. Neural plasticity: increasing the gain in pain. *Science* 2000; 288:1765–8.
- [72] Szczeplaniak WS, Møller AR. Evidence of decreased GABAergic influence on temporal integration in the inferior colliculus following acute noise exposure: a study of evoked potentials in the rat. *Neurosci Lett* 1995;196:77–80.
- [73] Quaranta A, Sallustio V, Scaringi A. Cochlear function in ears with vestibular schwannomas. In: Sanna M, Taibah A, Russo A, Mancini F, editors. *Third International Conference on Acoustic Neuroma and other CPA Tumors*. Rome, Italy: Monduzzi Editore; 1999. p. 43–50.
- [74] Jastreboff PJ, Jastreboff MM. Tinnitus retraining therapy (TRT) as a method for treatment of tinnitus and hyperacusis patients. *J Am Acad Audiol* 2000;11:162–77.
- [75] Brach JS, Van Swearingen JM, Lenert J, Johnson PC. Facial neuromuscular retraining for oral synkinesis. *Plast Reconstr Surg* 1997;99:1922–31.
- [76] Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science* 2000;288:1769–72.
- [77] Densert B, Sass K. Control of symptoms in patients with Meniere's disease using middle ear pressure applications: two years follow-up. *Acta Otolaryngol (Stockh)* 2001;121: 616–21.
- [78] Tonndorf J. The analogy between tinnitus and pain: a suggestion for a physiological basis of chronic tinnitus. *Hear Res* 1987;28:271–5.
- [79] Shea JJ, Emmett JR, Orchik DJ, Mays K, Webb W. Medical treatment of tinnitus. *Ann Otol Rhinol Laryngol* 1981;90:601–9.
- [80] Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971–9.

- [81] Jastreboff PJ, Brennan JF, Coleman JK, Sasaki CT. Phantom auditory sensation in rats: an animal model for tinnitus. *Behav Neurosci* 1988;102:811–22.
- [82] Møller AR, Pinkerton T. Temporal integration of pain from electrical stimulation of the skin. *Neurol Res* 1997;19:481–8.
- [83] Arendt-Nielsen L, Laursen RJ, Drewes AM. Referred pain as an indicator for neural plasticity. *Progress in Brain Research* 2002;129:343–56.
- [84] Carli G. Neuroplasticity and clinical pain. *Progress in Brain Research* 2000;129:325–30.
- [85]Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993;52:259–85.
- [86] Willer JC. Relieving effect of TENS on painful muscle contraction produced by an impairment of reciprocal innervation: an electrophysiological analysis. *Pain* 1988;32:271–4.
- [87] Price DD, Long S, Huitt C. Sensory testing of pathophysiological mechanisms of pain in patients with reflex sympathetic dystrophy. *Pain* 1992;49:163–73.
- [88] Brodal P. The central nervous system. New York: Oxford Press; 1998.
- [89] Levine RA. Somatic (craniocervical) tinnitus and the dorsal cochlear nucleus hypothesis. *Am J Otolaryngol* 1999;20:351–62.
- [90] Fowler EP. The illusion of loudness of tinnitus: its etiology and treatment. *Ann Otol Laryngol* 1942;52:275–85.
- [91] Reed GF. An audiometric study of 200 cases of subjective tinnitus. *Arch Otolaryngol* 1960;71:94–104.
- [92] Vernon J. The loudness of tinnitus. *Hear Speech Action* 1976;44:17–9.
- [93] Kvasnak E, Popelar J, Syka J. Discharge properties of neurons in subdivisions of the medial geniculate body of the guinea pig. *Physiol Res* 2000;49:369–78.
- [94] Hotta T, Kameda K. Interactions between somatic and visual or auditory responses in the thalamus of the cat. *Exp Neurol* 1963;8:1–13.
- [95] Szczepaniak WS, Møller AR. Interaction between auditory and somatosensory systems: a study of evoked potentials in the inferior colliculus. *Electroencephalogr Clin Neurophysiol* 1993;88:508–15.
- [96] Itoh K, Kamiya H, Mitani A, Yasui Y, Takada M, Mizuno N. Direct projections from dorsal column nuclei and the spinal trigeminal nuclei to the cochlear nuclei in the cat. *Brain Res* 1987;400:145–50.
- [97] Aitkin LM, Tran L, Syka J. The responses of neurons in subdivisions of the inferior colliculus of cats to tonal, noise and vocal stimuli. *Exp Brain Res* 1994;98:53–64.
- [98] Adolphs RD, Tranel H, Damasio H, Damasio AR. Fear and the human amygdala. *J Neurosci* 1995;15:5879–91.
- [99] LeDoux JE, Cicchetti P, Xagoraris A, Romanski LM. The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning. *J Neurosci* 1990;10:1062–9.
- [100] Marsh RA, Grose CD, Wenstrup JJ, Fuzessery ZM. A novel projection from the basolateral nucleus of the amygdala to the inferior colliculus in bats. *Soc Neurosci Abstr* 1999;25:1417.
- [101] McDonald AJ. Cortical pathways to the mammalian amygdala. *Prog Neurobiol* 1998;55:257–332.
- [102] Densert O. Adrenergic innervation in the rabbit cochlea. *Acta Otolaryngol (Stockh)* 1974;78:345–56.
- [103] Passe EG. Sympathectomy in relation to Meniere's disease, nerve deafness and tinnitus: a report of 110 cases. *Proc R Soc Med* 1951;44:760–72.
- [104] Adlington P, Warrick J. Stellate ganglion block in the management of tinnitus. *J Laryngol Otol* 1971;85:159–68.