Audiol Neurotol 2015;20(suppl 1):53–59
DOI: 10.1159/000380749

Revisiting the Cochlear and Central Mechanisms of Tinnitus and Therapeutic Approaches

Arnaud J. Noreña

Aix-Marseille University, CNRS UMR 7260, Marseille, France

Key Words

Auditory plasticity · Endocochlear potential · Middle ear · Outer hair cells · Spontaneous activity · Temporomandibular joint disorder · Tensor tympani

Abstract

This short review aims at revisiting some of the putative mechanisms of tinnitus. Cochlear-type tinnitus is suggested to result from aberrant activity generated before or at the cochlear nerve level. It is proposed that outer hair cells, through their role in regulating the endocochlear potential, can contribute to the enhancement of cochlear spontaneous activity. This hypothesis is attractive as it provides a possible explanation for cochlear tinnitus of different aetiologies, such as tinnitus produced by acute noise trauma, intense low-frequency sounds, middle-ear dysfunction or temporomandibular joint disorders. Other mechanisms, namely an excitatory drift in the operating point of the inner hair cells and activation of NMDA receptors, are also briefly reported. Central-type tinnitus is supposed to result from aberrant activity generated in auditory centres, i.e. in these patients, the tinnitus-related activity does not pre-exist in the cochlear nerve. A reduction in cochlear activity due to hearing loss is suggested to produce tinnitus-related plastic changes, namely cortical reorganisation, thalamic neuron hyperpolarisation, facilitation of non-auditory inputs and/or increase in central gain. These central changes can be associated with abnormal patterns of spontaneous activity in the auditory pathway, i.e. hyperactivity, hypersynchrony and/or oscillating activity. Therapeutic approaches aimed at reducing cochlear activity and/or tinnitus-related central changes are discussed.

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Introduction

Subjective tinnitus is an auditory perception not related to a sound source in the environment. Tinnitus is very prevalent in the general population and can be very bothersome [Ahmad and Seidman, 2004; McCormack et al., 2014]. Tinnitus can also be accompanied by other debilitating symptoms, such as hyperacusis (in 40% of tinnitus subjects), aural fullness, pain in the ear, nausea, dizziness, distorted hearing, headache and/or temporomandibular

joint disorders [Dauman and Bouscau-Faure, 2005; Ramirez et al., 2008; Westcott et al., 2013]. Tinnitus can result from many different aetiologies. A major challenge in tinnitus research is to identify the different causes of tinnitus in order to develop therapies specific for each tinnitus subtype [Noreña, 2011, 2012a; Noreña and Farley, 2013]. This article is aimed at providing a short review on putative mechanisms of tinnitus.

Peripheral or Cochlear Tinnitus

Cochlear-type tinnitus can be defined as a tinnitus subtype resulting from an aberrant activity generated at the periphery of the auditory system, i.e. before or at the cochlear nerve level. The activity induced by cochlear-type tinnitus can be compared to the neural activity produced by a suprathreshold acoustic stimulus. The activity is first increased in the cochlear nerve and then propagates all the way up to the auditory cortex. Whether this neural activity leads to an auditory perception depends on the level of this neural activity and top-down modulation (i.e. attention) [Noreña and Farley, 2013; McKenna et al., 2014].

While many mechanisms can theoretically result in tinnitus-related activity in the cochlear nerve [Tonndorf, 1981, 1987; Jastreboff, 1990; LePage, 1995; Patuzzi, 2002; Ruel et al., 2008], only a few are further described here.

Modulation of the Endocochlear Potential. Cochlear spontaneous activity is strongly coupled to the endocochlear potential (EP) [Sewell, 1984]. Because some of the mechano-electric transduction (MET) channels of the inner hair cells are opened at rest, an increase or decrease in the EP can either depolarise or hyperpolarise the inner hair cells, respectively. The depolarisation of inner hair cells triggers a cascade of events (opening of the voltage-gated Ca^{2+} channels, intracellular influx of Ca^{2+} and fusion of the synaptic ribbon to the plasmatic membrane) leading to glutamate release and depolarisation of cochlear fibres [Hudspeth, 1985; Moser et al., 2006].

Outer hair cells can play a role in regulating the EP by allowing a current shunt through their MET channels. By limiting or preventing this current shunt, a reduction in the opening probability of MET channels can raise the EP. The opening probability of MET channels depends on stereocilium bundle deflection [Avan et al., 2013]. Any shift in the operating point of MET channels toward the scala tympani (hyperpolarisation direction) can raise the EP [Patuzzi, 2002, 2011].

Intense low-frequency sound presented for about 1 min is known to generate a form of low-frequency ('roaring noise') tinnitus [Patuzzi and Wareing, 2002; Drexler et al., 2014]. The intense low-frequency sound is supposed to shift the operating point of MET channels toward the hyperpolarising side of the transfer function, which could lead to an increase in EP. Interestingly, it has been proposed that the enhanced concentration of K^+ may produce an endolymphatic hydrops by causing water influx into the scala media through aquaporins [Kirk and Patuzzi, 1997; Salt, 2004].

Very-low-frequency sounds (<10 Hz) and spontaneous contractions of the middle-ear muscles have been reported to be accompanied by changes in EP and longitudinal movements of the endolymph [Salt and DeMott, 1999]. This study establishes a potential connection between the middle-ear pressure, or 'status' (presence or absence of a displacement of the stapes into the scala vestibuli), and the inner ear. It has been speculated that outer hair cells can 'sense' small pressure changes in the inner ear through the operating point of their MET channels [Bell, 2011]. This hypothesis provides a plausible mechanism that could account for tinnitus related to the tonic tensor tympani syndrome [Westcott et al., 2013] and temporomandibular joint disorders [Ramirez et al., 2008].

Finally, it has been suggested that acute noise trauma alters MET channels, which may reduce their opening probability and give rise to an increased EP [Patuzzi, 2002].

Excitatory Drift in the Operating Point of the Inner Hair Cells. Like outer hair cells, inner hair cells have a tuft of stereocilia at their apex with MET channels. The opening probability of MET channels depends on the bending of stereocilia, which is related to the distance between the tectorial membrane and the inner hair cells. It has been proposed that any condition shifting the relative position of the tectorial membrane toward the inner hair cells can lead to prolonged depolarisation of inner hair cells [LePage, 1995]. This excitatory drift in the operating point of inner hair cells may result from a pressure increase in the scala media, detachment of the tectorial membrane from the tips of outer hair cells, outer hair cell degeneration or stereocilium damage [LePage, 1995].

Acute noise trauma, for instance, has been shown to alter stereocilium rootlets [Liberman and Dodds, 1987], which are known to be involved in stereocilium stiffness [Saunders et al., 1985; Kitajiri et al., 2010]. These alterations in the stereocilia may account for the acute increase in cochlear spontaneous activity after noise trauma [Liberman and Dodds, 1987].

NMDA Receptors. Salicylate-induced tinnitus has been suggested to result from an increased cochlear firing rate caused by the activation of the NMDA receptors [Guitton et al., 2003; Ruel et al., 2008]. Due to its inhibition of cyclooxygenase activity, it is suggested that salicylate leads to an accumulation of arachidonic acid in the plasmatic membrane of cochlear fibres. This may alter the mechanic properties of the membranes and increase the opening probability of NMDA receptors [Puel and Guitton, 2007]. Activation of NMDA receptors might also be involved in noise-induced tinnitus, at least at an acute stage, i.e. within a few days after noise trauma [Guitton and Dudai, 2007].

Central Tinnitus

Central-type tinnitus is underpinned by neural activity that is generated in the auditory centres, namely when the tinnitus-related activity does not 'pre-exist' in the cochlear nerve. For this form of tinnitus, the auditory centres play an active role in generating the tinnitus-related activity. This is likely the case for chronic tinnitus induced by noise trauma, as cochlear activity has been shown to be reduced after the trauma [Liberman and Dodds, 1984; Heinz and Young, 2004]. More recently, it was shown that moderate noise trauma can alter the synaptic ribbons of inner hair cells and trigger the degeneration of high-threshold cochlear fibres [Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013]. Moreover, tinnitus is largely prevalent in subjects with profound hearing

loss [Quaranta et al., 2004; Baguley and Atlas, 2007], where cochlear nerve activity is likely very low or absent [Hartmann et al., 1984; Shepherd and Javel, 1997]. Finally, while cochlear nerve section can abolish tinnitus in some cases, tinnitus can remain in other cases [House and Brackmann, 1981; Barrs and Brackmann, 1984; Pulec, 1995]. Altogether, these results argue for a causal role necessarily played by the auditory centres for generating the tinnitus-related activity, at least in some subtypes of tinnitus.

Many central mechanisms have been proposed to account for the generation of tinnitus-related activity. Most, if not all, of these mechanisms are supposed to be triggered by a reduction in cochlear activity [Noreña, 2012a]. One notes that cochlear damage is not necessary to produce the tinnitus-related central changes, as conductive hearing loss, which preserves hair cells and cochlear fibres, has been reported to induce tinnitus [Ayache et al., 2003; Midani et al., 2006; Schaette et al., 2012]. These latter studies refine our understanding of the tinnitus-related central changes, which may be triggered by a shift in the distribution of sensory inputs toward lower values. Hearing loss has been shown to lead to reorganisation of the tonotopic map [Robertson and Irvine, 1989; Noreña and Eggermont, 2005], hyperpolarisation of thalamic cell membranes [Jeanmonod et al., 1996; Llinás et al., 1999, 2005], facilitation of non-auditory inputs [Shore et al., 2007] and/or increases in neural sensitivity or gain [Schaette and Kempter, 2006; Noreña, 2011]. These central changes can then alter the pattern of neural firing, producing neural hyperactivity at cortical and sub-cortical levels [Kaltenbach and Afman, 2000; Noreña et al., 2003; Mulders and Robertson, 2009; Kalappa et al., 2014; Vogler et al., 2014], hypersynchrony in the cortex [Noreña et al., 2003; Noreña and Eggermont, 2006; Tass et al., 2012] and/or changes in cortical or thalamocortical oscillating activity [Jeanmonod et al., 1996; Llinás et al., 2005; Weisz et al., 2005; Adjamian et al., 2012].

Cochlear ablation carried out a few weeks after noise trauma has been found to abolish the noise-induced hyperactivity in the inferior colliculus [Mulders and Robertson, 2009]. On the other hand, cochlear ablation performed 12 weeks after noise trauma does not alter the noise-induced central hyperactivity [Mulders and Robertson, 2011]. These studies suggest that two forms of central tinnitus can be distinguished. In one form, the central tinnitus-related activity can remain dependent on the cochlear spontaneous activity (i.e. peripheral-dependent central tinnitus); in another form, the tinnitus-related activity can be 'centralised', i.e. independent from the cochlear spontaneous activity (i.e. peripheral-independent central tinnitus) [Noreña, 2011].

Therapeutic Approaches

Reducing the Cochlear Spontaneous Activity. The hypothesis has been developed suggesting that middle ear disorders could give rise to an increase in EP and, as a consequence, cochlear tinnitus, as mentioned earlier. In those cases, fixing the somatic problems (contraction of the tensor tympani or temporomandibular joint disorders, for instance) should suppress tinnitus [Ramirez et al., 2008; Riga et al., 2010; Westcott et al., 2013].

It has been proposed that the activation of postsynaptic NMDA receptors at the synapses between inner hair cells and cochlear fibres could lead to cochlear tinnitus-related activity. A straightforward approach is then to block these receptors with antagonists [Guitton et al., 2003; Puel and Guitton, 2007; Ruel et al., 2008]. Because NMDA receptors are widespread in the brain, antagonists

Fig. 1. Effects of extracochlear electric stimulation on the activity of a single unit in the inferior colliculus recorded 2 weeks after noise trauma. The characteristic frequency of this unit is 10.4 kHz. First row: spontaneous activity (68 spikes/s, which is elevated and might correspond to the tinnitus-related activity). Second row: effects of

electrical stimulation (500-ms stimulation every 2 s) with negative current on neural activity. Third row: effects of electrical stimulation (500-ms stimulation every 2 s) with positive current on neural activity. This example shows that the negative current is excitatory, whereas the positive current is inhibitory. FR = Firing rate.

of NMDA receptors should be administrated as locally as possible to avoid any side effects, i.e. through intratympanic perfusion [Meyer, 2013]. A few studies have reported some benefits of this approach on tinnitus patients [Wenzel et al., 2010; Suckfuell et al., 2014; Van de Heyning et al., 2014].

It is also conceivable to reduce the cochlear spontaneous activity by electrical stimulation of the ear. Indeed, electrical stimulation can change the membrane potential of ‘excitable’ cells (hair cells and cochlear fibres) in the ear [Javel and Shepherd, 2000]. The direction of the effect, whether the electrical stimulation results in a depolarisation or hyperpolarisation, depends on the polarity of the electric current. A positive (anodic) current provided at the round window or in the scala tympani produces a displacement of the negative charges from the extracellular environment of cochlear fibres and hair cells nearby the stimulating electrodes toward the electrodes. The movement of negative charges away from inner hair cells and cochlear fibres is supposed to hyperpolarise them, leading to a reduction of glutamate release and/or cochlear spontaneous firing [Konishi et al., 1970; Evans and Borerwe, 1982]. In a recent study, a positive current applied at the round window could suppress the putative tinnitus-related activity in the inferior colliculus, with only a modest effect, if any, on sound-induced activity [Noreña et al., 2015] (fig. 1). This study may account for the tinnitus suppression produced by the positive current delivered at the promontory or the round window [Cazals et al., 1978; Portmann et al., 1979]. This approach is attractive as it is aimed at modulating cochlear activity without making any a priori assumptions on tinnitus mechanisms. It could be used to abolish tinnitus for a prolonged period of time (i.e. hours to days) and potentially at will (like a ‘switch’). We are currently working on the issue of

reducing the putative tinnitus-related activity from innocuous charge-balanced electrical stimulation to avoid the well-known harms produced by direct current on tissues [Shepherd et al., 1999; Merrill et al., 2005].

Targeting the Tinnitus-Related Central Changes through Auditory Stimulation. Some tinnitus subtypes have been suggested to result from the central changes triggered by a reduction in cochlear activity (due to cochlear damage). While cochlear damage cannot be repaired, it is, however, believed that the tinnitus-related central changes can be reversed. Many approaches have been developed to achieve this goal, each depending on a particular view about the tinnitus mechanisms (fig. 2) [Noreña, 2012a].

Approaches aimed at reducing the putative overrepresentation of tinnitus frequency (the hypothesised cause of tinnitus) have been developed [Flor et al., 2004; Herraiz et al., 2007; Engineer et al., 2011; De Ridder et al., 2014]. However, as the tinnitus frequency is usually outside and above the frequency range of the hearing loss [Noreña et al., 2002; Sereda et al., 2014], it seems very unlikely that it is overrepresented in the auditory cortex (fig. 2b, c). These approaches may still have a beneficial effect on tinnitus.

Assuming that tinnitus results from central hyperactivity, an approach has been developed to reduce the tinnitus-related activity through lateral inhibition. Lateral inhibition is ‘concentrated’ on the hyperactive neurons underpinning tinnitus through an acoustic stimulation (music) with a spectral notch centred on the tinnitus frequency. This method has been shown to produce some improvement in tinnitus (fig. 2d) [Okamoto et al., 2010].

Recently, an approach has been proposed to reduce the hyper-synchrony potentially causing tinnitus [Tass et al., 2012]. An acoustic sequence is presented to tinnitus subjects consisting of

Fig. 2. Summary of the different acoustic approaches which aim at reversing the tinnitus-related central changes. The schematic at the top (**a**) shows an idealised audiogram with high-frequency hearing loss. The other rows show the spectrum of the acoustic stimuli developed to reverse the tinnitus-related central changes. **b, c** Spectrum of acoustic stimuli designed to reduce the cortical representation of tinnitus. These approaches assume that tinnitus frequency is overrepresented (i.e. located at the edge frequency of hearing loss – see vertical dashed line), which is very unlikely (see text). **d** Spectrum of a notched stimulus aimed at suppressing the tinnitus-related activity through lateral inhibition. Inset: the spectrogram of the acoustic sequence is shown as the temporal properties of the acoustic sequence are also critical in this approach. **e** Spectrum of the acoustic stimulus aimed at restoring normal sensory inputs, i.e. those that existed before hearing loss. The vertical dotted lines show where the dominant pitch of tinnitus is expected, i.e. at the edge frequency of hearing loss (**b–c**) and above this latter frequency (**d–f**). oct = Octave.

non-simultaneous tone pips at about the same frequency as the tinnitus frequency (fig. 2e) [Adamchic et al., 2014]. This acoustic sequence aims at achieving asynchronous activation of the tinnitus-related network in order to reduce the connectivity within the network and abolish the hypersynchrony. This method has been reported to improve tinnitus [Tass et al., 2012].

Finally, assuming that the tinnitus-related central changes are triggered by a reduction in cochlear activity, other approaches suggested to stimulate the auditory system so as to restore the pre-hearing loss distribution of sensory inputs and reverse the tinnitus-related central changes [Noreña et al., 2002; Noreña and Eggermont, 2005, 2006; Schaette and Kempster, 2006; Noreña, 2011, 2012]. This could possibly be achieved from hearing aids or customised acoustic stimulation with long-term spectrum corresponding to the hearing loss (fig. 2f) [Del Bo and Ambrosetti, 2007; Noreña and Chéry-Croze, 2007; Schaette et al., 2010; Parazzini et al., 2011]. The frequency range of amplification provided by hearing loss is, however, limited to frequencies below approximately 6 kHz. Interestingly, tinnitus reduction produced by hearing aids is significantly stronger when the tinnitus pitch is below 6 kHz [Schaette et al., 2010].

Cochlear implants, which are designed to restore hearing through electrical stimulation, have an impact on tinnitus. The tinnitus reduction often reported for individuals after cochlear implantation [Quaranta et al., 2004; Baguley and Atlas, 2007; Tyler et al., 2008; Van de Heyning et al., 2008] may result from the partial reversal of the tinnitus-related central changes [Noreña, 2011, 2012b]. In one study, electrical stimulation with high-rate pulse

trains (5 kHz), which was delivered through a cochlear implant or from a ball electrode placed on the round window, was used to restore the normal cochlear spontaneous activity (suggested to be a ‘code for silence’) [Rubinstein et al., 2003]. They report that electrical stimulation produced tinnitus suppression in one third of the cochlear implant subjects examined and in 5 of 11 transtympanic subjects in the absence of auditory perception. In 3 intratympanic subjects, electrical stimulation produced auditory perception at the beginning of the stimulation only. Interestingly, the time course of the tinnitus reduction paralleled the adaptation of the auditory perception. A possible interpretation of these results is that the electrical stimulation used in this study can be excitatory at the beginning of the stimulation and ‘inhibitory’ thereafter due to strong neural adaptation. These latter effects of electrical stimulation have been reported in the cochlear nerve in cats [Litvak et al., 2001]. Furthermore, the findings from Rubinstein et al. [2003] suggest that tinnitus may disappear when cochlear and/or central tinnitus-related activity is abolished.

In summary, most of the therapy methods described in this review have been reported to improve tinnitus. This global ‘efficiency’ is surprising as the approaches vary substantially. These results suggest that stimulating the auditory system may be beneficial for tinnitus conditions, whatever the long-term spectrum of the stimulation. Other studies, however, suggest that the long-term spectrum of the auditory stimulation should compensate the hearing loss as closely as possible [Noreña and Eggermont, 2005, 2006; Moffat et al., 2009; Schaette et al., 2010; Punte et al., 2013]. Overall, auditory stimulation may induce only a partial reversal of the tin-

nitus-related central changes. This may account for the fact that tinnitus is only rarely abolished by auditory stimulation [Del Bo and Ambrosetti, 2007; Davis et al., 2008; Van de Heyning et al., 2008]. Structural changes in the central auditory system triggered by lesions of the sensory epithelium may be difficult to reverse [Darian-Smith and Gilbert, 1994; Holtmaat and Svoboda, 2009; Zheng et al., 2011]. The presence of dead regions [Weisz et al., 2006; Etchelecou et al., 2011] and/or the degeneration of cochlear fibres [Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013] may also prevent auditory stimulation from restoring normal patterns of sensory inputs to the auditory centres. Finally, the tinnitus-related network may become progressively 'centralised', i.e. independent from the cochlear inputs [Mulders and Robertson, 2011]. This could be, at least in part, due to the enhanced excitatory modulation played by the somatosensory system after hearing loss [Shore et al., 2007].

Conclusion

In the present review, it has been suggested that at least three different subtypes of tinnitus can be distinguished: cochlear tinnitus, peripheral-dependent central tinnitus and peripheral-independent central tinnitus.

Many peripheral mechanisms can possibly enhance the cochlear activity and lead to cochlear tinnitus. The hypothesis suggesting a pivotal role of outer hair cells in regulating the EP through the opening probability of their MET channels seems plausible [Patuzzi, 2002]. In particular, this mechanism may account for acute tinnitus after noise trauma and chronic tinnitus in subjects without cochlear lesions and/or following middle-ear dysfunction. Cochlear mechanisms, however, do not account for cases of tinnitus associated with reduced or absent cochlear activity. Central tinnitus models, on the other hand, are able to account for these tinnitus subtypes. Conversely, central tinnitus models hardly account for acute tinnitus induced immediately after noise trauma [Loeb and Smith, 1967; Atherley et al., 1968] as the noise-induced hyperactivity in the auditory centres takes a few minutes to hours to develop [Noreña and Eggermont, 2003; Mulders and Robertson, 2013]. It has been proposed, however, that acute noise-induced tinnitus could be related to the cortical hypersynchrony resulting from the rapid unmasking of thalamocortical connections after noise trauma [Noreña and Eggermont, 2003].

Only a few therapeutic approaches have been reviewed in this article. In particular, the cognitive therapies based on relaxation, diversion of attention and/or habituation have not been explored [Jastreboff, 2007; Cima et al., 2014; McKenna et al., 2014]. For cochlear and peripheral-dependent central tinnitus, a reduction in the cochlear spontaneous activity is believed to reduce tinnitus. For peripheral-independent central tinnitus, reversing the tinnitus-related central changes is expected to improve tinnitus.

Disclosure Statement

No conflict of interest.

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Corresponding author:
 Arnaud J. Noreña
 Centre St-Charles, Pôle 3C – Case B
 3, place Victor Hugo
 FR-13331 Marseille Cedex 03 (France)
 E-Mail arnaud.norena@univ-amu.fr