Mechanisms of tinnitus

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The generation of tinnitus is a topic of much scientific enquiry. This chapter reviews possible mechanisms of tinnitus, whilst noting that the heterogeneity observed within the human population with distressing tinnitus means that there may be many different mechanisms by which tinnitus can occur. Indeed, multiple mechanisms may be at work within one individual. The role of the cochlea in tinnitus is considered, and in particular the concept of discordant damage between inner and outer hair cells is described. Biochemical models of tinnitus pertaining to the cochlea and the central auditory pathway are considered. Potential mechanisms for tinnitus within the auditory brain are reviewed, including important work on synchronised spontaneous activity in the cochlear nerve. Whilst the number of possible mechanisms of tinnitus within the auditory system is considerable, the identification of the physiological substrates underlying tinnitus is a crucial element in the design of novel and effective therapies.

Hypotheses regarding mechanisms of tinnitus generation abound. Given the heterogeneity observed in the tinnitus population, it may be considered that no single theory, model or hypothesis will explain the presence of tinnitus in all those affected. Thus, the mechanisms described in this chapter are not mutually exclusive, and multiple mechanisms may be present in an individual with tinnitus. The focus of this review is upon physiological mechanisms of tinnitus generation rather than the psychological impact that tinnitus may have, or therapies and treatments.

The word tinnitus derives from the Latin tinere meaning 'to ring', and in English is defined as 'a ringing in the ears'. In an attempt at a scientific definition, McFadden considered that: 'tinnitus is the conscious expression of a sound that originates in an involuntary manner in the head of its owner, or may appear to him to do so'. This definition has been widely adopted.

Tinnitus is a common experience in adults and children. Adult data from the MRC Institute of Hearing Research indicate that, in the UK, 10% of adults have experienced prolonged spontaneous tinnitus, and that in 5% of adults tinnitus is reported to be moderately or severely annoying. In 1% of the adult population, tinnitus has a severe effect on quality of life. The incidence data from the MRC study indicate that 7% of the UK adult population have consulted their doctor about tinnitus, and 2.5% have...
attended a hospital with regard to tinnitus. Up to one-third of children experience occasional tinnitus, and in approximately 10% tinnitus has been bothersome.

A complex relationship between epidemiological factors and tinnitus has been identified. The prevalence of tinnitus increases with age and with hearing impairment. Women are more likely to report tinnitus than men, and occupational noise and lower socio-economic class are also associated with increased tinnitus. These factors are not independent of each other, and further work is needed in this area.

A large number of descriptors of tinnitus have been reported, the most common being hissing, sizzling and buzzing, these reflecting the clinical finding that tinnitus is usually high pitched. An individual may localise tinnitus to one ear or other, to both, within the head or occasionally external to the head. In a clinical context, many individuals may hear more than one tinnitus sound.

Tinnitus is an element of the symptom profile of several significant otological pathologies (such as otosclerosis, vestibular schwannoma and Menière's disease) that necessitate medical or surgical treatment. Whilst such conditions are rare within both the general and tinnitus-complaint populations, there is a consensus that an informed clinical opinion should be sought by an individual with troublesome tinnitus (especially when unilateral) in order to exclude such pathologies. This review does not consider pathology-specific mechanisms other than the cochlear dysfunction implicated in sensorineural hearing loss.

Cochlear models

Any model which considered the cochlea in isolation from the rest of the auditory pathway in relation to tinnitus would not now be considered adequate, but there are situations where cochlear dysfunction has been implicated in tinnitus generation.

Spontaneous oto-acoustic emissions

The concept that a normal healthy cochlea may produce low intensity tonal or narrow-band sound in the absence of any acoustic stimulation (spontaneous oto-acoustic emissions, SOAEs) was introduced by Gold in 1948 as an element of a model of active processes within the cochlea. The identification of such activity (see Kemp this volume) was greeted with enthusiasm by the scientific community concerned with tinnitus as ‘our hope was that they corresponded to their owner’s tinnitus and thus, at long last, we could measure tinnitus objectively’.
This hope was not well founded, as it became clear that whilst 38–60% of normal-hearing adults have measurable SOAEs, the majority of such individuals are not aware of this activity. Penner and Burns noted that when SOAEs do occur in the ear of a tinnitus patient, they rarely correspond to the judged frequency of the tinnitus. These authors considered that if a SOAE could be suppressed by a suitable low-level external tone without affecting the tinnitus perception, and, conversely, if tinnitus could be masked in an individual without affecting the SOAE, then the inference of physiological independence could be made. This suppression/masking paradigm has been used to determine the incidence of tinnitus complaint caused by SOAEs. Penner found that 4.1% of a series of tinnitus patients (n = 96) had tinnitus originating as an SOAE. Baskill and Coles found an incidence of 2%, and Coles (cited in Penner) of 4.5%.

One additional piece of evidence that SOAEs are not largely responsible for tinnitus generation is as follows. SOAEs are largely abolished by aspirin (salicylate), but tinnitus perception is not generally improved by salicylate, there being only one report of such an experience, this in a case where SOAE and tinnitus were demonstrably linked. Penner notes that the treatment of SOAE-generated tinnitus with salicylate is done at the risk of ototoxic hearing loss and the possible generation of new tinnitus perceptions.

**Discordant damage of IHC and OHC**

Jastreboff noted that intense noise and ototoxic agents initially damage the basal turn of the cochlea, and outer hair cells (OHCs), and only later affect inner hair cells (IHCs) if continued or repeated, IHCs being more resistant to such damage. The inference was made that, within a partially affected organ of Corti, there will be an area with both OHCs and IHCs affected, an area with OHCs are affected but IHCs are intact, and an area with both intact. In the second of these three categories, the coupling between the tectorial membrane and the basilar membrane would be affected, to the extent that the tectorial membrane might directly impinge upon the cilia of the IHCs, thus causing them to depolarise. Clinical support for such modification of auditory afferent activity leading to tinnitus perception has been cited, in that some patients with tinnitus and high-frequency hearing loss match their tinnitus frequency to the point at which the loss begins. The role that increased neural activity in the auditory periphery may have in tinnitus generation is considered in detail below. Jastreboff went on to consider not only the afferent activity generated by the IHCs, but also the possibility that afferent activity of the IHCs might be interpreted in the
light of attempted (but failed) reduction of cochlear gain via OHCs, giving rise to increased perceived intensity. It was further suggested that this model might apply to both permanent and temporary discordant damage, the example of temporary damage being temporary tinnitus associated with temporary threshold shift following noise exposure. Chery-Croze et al\textsuperscript{21} noted that, in an area where IHC damage was present, any efferent inhibition of the OHCs in that area will be reduced due to the reduced afferent input. That efferent innervation may be shared with neighbouring OHCs partnering undamaged IHCs, due to the diffuse nature of efferent innervation (one fibre for 20–30 OHCs), and so the undamaged area neighbouring the damaged IHCs may also have reduced efferent inhibition, giving rise to a highly active area of the basilar membrane, resulting in tonal tinnitus.

LePage\textsuperscript{22} suggested an alternative mechanism by which an area of the basilar membrane with damaged OHCs but intact IHCs might contribute to tinnitus generation. The role of the normal OHCs in fixing the operating point of IHCs was considered, that is an ability of OHCs to control the sensitivity of IHCs by setting the operating point on the IHCs’ transfer characteristic to a value which the brain normally interprets as no sound. This point would not actually correspond to zero sound input, but a sound level regarded as background. A loss of motility in OHCs might reduce the ability to set the operating point of the IHCs appropriately, thus causing a ‘virtual’ sound input, so that this normally inaudible activity might be perceived as tinnitus. If this were to occur over a short length of the basilar membrane, the perception would be interpreted according to the tonotopic frequency normally transduced at that point, and hence would be tonal. LePage notes that if there were functional OHCs adjacent to the dysfunctional OHCs, then no loss of audiometric sensitivity might be evident. Zenner and Ernst\textsuperscript{23} suggested that tinnitus generated by such a mechanism should be classified as ‘DC motor tinnitus’.

A further role for OHC in tinnitus has been suggested by Patuzzi\textsuperscript{24}, who noted that OHC dysfunction may cause excessive release of neurotransmitter from IHCs following an increase in the endocochlear potential. This phenomenon might then lead to a ‘rate tinnitus’, so called because of the excessive rate of glutamate release from IHCs. Patuzzi predicted that the tinnitus percept would have a ‘hiss’ quality.

Biochemical models

A biochemical model of peripheral tinnitus has recently been proposed\textsuperscript{25} based partly on the clinical observation that adult humans with distressing tinnitus have experiences of agitation, stress and anxiety, and
partly on cochlear neurochemistry. Endogenous dynorphins (associated with stress) are postulated to potentiate the excitatory function of glutamate within the cochlea, mimicking the action of sodium salicylate in increasing spontaneous neural activity.

The biochemistry of the central auditory system has also been considered in the tinnitus literature. A role for serotonin (5-HT) in persistent tinnitus was postulated by Simpson and Davies26, based on the consideration that disrupted or modified 5-HT function might cause a reduction in auditory filtering abilities and in tinnitus habituation (see later). The identification of a role of 5-HT in persistent distressing tinnitus is important as it may facilitate the development of effective pharmacological intervention. The need for investigation of the effect of selective serotonin re-uptake inhibitors upon tinnitus is urgent27.

Non-cochlear mechanisms of tinnitus generation

Considerable attention has been paid to the possible involvement of cochlear mechanisms in tinnitus generation, but in recent years the interest of the scientific community has shifted towards retro-cochlear and central mechanisms16,28–31. In many cases, the models and hypotheses proposed do not preclude a role for the cochlea, but have as their primary concern neural mechanisms of tinnitus generation and persistence.

Jastreboff neurophysiological model

In a review of tinnitus from a neurophysiological perspective, Jastreboff16 considered a role for ‘signal recognition and classification circuits’ in persistent tinnitus, that function as neural networks becoming tuned to the tinnitus signal, even when that signal is transitory, fluctuating or intermittent. It was suggested that cochlear processes might be involved in the generation of weak tinnitus-related activity, but since the majority of individuals with normal hearing perceive tinnitus-like sound in quiet surroundings32, it was not necessary for a lesion of the auditory system to be present for tinnitus to be heard. The Jastreboff ‘neurophysiological model’, which involves the auditory perceptual, emotional and reactive systems involved in tinnitus, was published in 199633 and in slightly more detailed form (Fig. 1) in 199934. In many individuals after a short period of awareness of tinnitus-related activity, a process of habituation occurs, such that the activity is no longer consciously perceived. However, in cases where there is some ‘negative emotional reinforcement’, described as fear, anxiety or tension, limbic system and autonomic activation cause the activity to be enhanced and perception
The distinction between the perception of, and the behavioural and emotional reaction to, tinnitus was explicit, as was the potential for a feedback loop between these processes. A treatment protocol arising from this perspective, and based upon facilitating habituation to both the tinnitus signal and to the reaction to that perception, has been entitled Tinnitus Retraining Therapy. The Jastreboff model has been widely accepted as a synthesis that has utility for patients, clinicians and researchers alike. Whilst direct empirical evidence to support this model has not been forthcoming, the concepts involved are congruent with a modern understanding of the auditory system. A potential criticism is that the model does not represent the full complexity and dynamism of the human auditory system, but if the primary aim was a model of tinnitus that was easily understood by patients then this may have been intentional.

Increased neural activity

Evans et al noted that then contemporary theories of tinnitus generation made the assumption, either implicit or explicit, that it was associated with spontaneous overactivity of the cochlear nerve. This was at odds with the literature which indicated that experimentally induced chronic cochlear pathology resulted in a decrease in such spontaneous activity. Such a decrease had been reported by Kiang et al on the basis...
of a study involving kanamycin-deafened cats. Evans et al. reported that doses of salicylate in the cat equivalent to blood-concentration doses known to induce tinnitus in humans (in excess of 300-400 mg/l) had the effect of increasing spontaneous activity. Tyler noted the different methodology of these studies, and that the recording from single units in the cochlear nerve might miss hyperactivity occurring elsewhere. Eggermont also considered the discrepancy between these findings, and concluded that increased spontaneous activity in the human cochlear nerve was unlikely to be involved in tinnitus generation (assuming that animal data can be applied to humans) since tinnitus-inducing events in humans are as likely to reduce spontaneous activity as increase it.

Increased neural activity at levels above the cochlear nerve may be implicated in tinnitus generation. Increases in spontaneous activity in the dorsal cochlear nucleus (DCN) in the golden hamster after intense sound exposure have been reported. Salvi et al. subjected chinchillas to intense sound exposure (2 kHz tone, 105 dB SPL, 30 min) and reported increases of spontaneous activity in the inferior colliculus and the dorsal cochlear nucleus; in addition, they noted tonotopic reorganisation in these structures. Increased activity in the inferior colliculus has also been reported after salicylate administration in the rat and the guinea pig. Chen et al. studied the effect of intense sound exposure (125 dB SPL, 10 kHz tone, 4 h) on spontaneous activity in the DCN of the rat. They found an increase in bursting spontaneous activity and a decrease in regular (simple spiking) spontaneous activity. The authors suggested that such activity might represent increased auditory efferent activity.

Increased cortical activity in the gerbil following salicylate administration has been demonstrated using 2-deoxyglucose methods and c-fos immunochemistry, one study using impulse noise as well as salicylate to induce cochlear dysfunction. Wallhausser-Franke and Langner also noted evidence of increased activity in the amygdalae of these animals, and considered this a response to induced tinnitus, though they noted that the changes may have been produced by the stress of the animals. Langner and Wallhauser-Franke proposed a model for tinnitus generation based on these findings. The lack of increased activity in the ventral cochlear nucleus (VCN) after salicylate administration was claimed as evidence that the reported effects of salicylate are not due to increased afferent activity in the cochlear nerve. The altered activity reported in the DCN was suggested to result either from increased efferent activity from the cortex or inferior colliculus (IC), or from a lack of inhibition from other cochlear nucleus units. The amplification of spontaneous activity within this feedback loop, influenced also by processes of attention (involving the reticular
formation) and the limbic system (specifically the amygdala) was thought to be the cause of tinnitus perception.

A mechanism of disinhibition in the IC and DCN has been proposed\textsuperscript{30,50}. In the DCN type II/III, interneurones act in an inhibitory manner upon spontaneously active type IV neurones\textsuperscript{30}. If these inhibitory interneurones have reduced afferent input due to peripheral auditory dysfunction, there may be a loss of inhibition of the spontaneous activity of the type IV neurones, thus resulting in abnormally high spontaneous activity which might be audible. Eggermont\textsuperscript{30} furthered this proposal, suggesting, after Moller\textsuperscript{51}, additional disinhibition in the IC.

Synchronisation of spontaneous neural activity

Eggermont\textsuperscript{30} has reviewed the evidence for a theory that tinnitus may result from the imposition of a temporal pattern upon stochastic cochlear nerve activity. Hudspeth and Corey\textsuperscript{52} reported that, in the saccular hair cells of the bull frog, an increase in the concentration of extracellular calcium could lead to increased firing. Eggermont\textsuperscript{29} proposed that if such a calcium-induced increase were present in dysfunctional human cochleae, then it might lead to enhanced neurotransmitter release from IHC, and thence to increased activity in auditory nerve fibres, some of the spikes occurring in bursts. This pattern of activity (burst-firing) may mimic that seen in response to sound stimulation. Burst-firing can occur in the cat auditory nerve after exposure to kanamycin\textsuperscript{16}, and in the rat inferior colliculus after salicylate administration\textsuperscript{42}. Increased burst-firing in the rat DCN following intense sound exposure has also been reported\textsuperscript{44}. Kaltenbach\textsuperscript{31} argued that a link between such bursting activity and tinnitus perception is problematic, in the light of the finding of Ochi and Eggermont\textsuperscript{53,54} that, in the cat, no increase in cortical bursting activity is demonstrated after administration of salicylate or quinine. It is possible, however, that bursting activity in the auditory periphery could be re-coded as a rate change in more central nuclei.

Eggermont\textsuperscript{50} proposed that the synchronised activity of a small number of fibres in the auditory periphery may give rise to a sensation of sound, and thus of tinnitus. Moller\textsuperscript{55} drew an analogy with hemifacial spasm and trigeminal neuralgia patients, noting that the surgical decompression of vessels impinging upon the Vth cranial nerve relieved trigeminal neuralgia, and upon the VIIth cranial nerve relieved hemifacial spasm. Moller noted that these cranial nerves were sensitive to such compression at the root entry zone, where they were covered by myelin. He hypothesised that compression of the nerve caused cross-talk between nerve fibres, the breakdown of the myelin insulation of the
nerve fibres establishing ephaptic coupling between them. This concept was applied to the cochlear-vestibular nerve, which is covered by central myelin for the majority of its length, and hence is vulnerable to compression from blood vessels or tumours impinging upon the nerve, such as vestibular schwannoma. Such compression and consequent ephaptic coupling might lead to tinnitus perception, if synchronisation of the stochastic firing in the human cochlear nerve is perceived as sound. Eggermont\textsuperscript{29} modelled the effect of ephaptic interaction between fibres of the auditory nerve, and proposed that the effect of the interaction was to increase the number of interspike intervals around 10 ms. He concluded that the ephaptic interaction model had a 'potential real-life parallel in the demyelinating effects of tumours of the eighth nerve' (e.g. vestibular schwannoma).

Several terms have been used for such measures of synchronised activity - ensemble spontaneous neural activity (ESNA)\textsuperscript{56}, average spectrum of electrophysiological cochlear activity (ASECA)\textsuperscript{57}, ensemble spontaneous activity (ESA)\textsuperscript{58}, and spectrum of background neural noise (SNN)\textsuperscript{59}. Evidence for synchronised spontaneous neural activity associated with tinnitus is emergent. Martin \textit{et al}\textsuperscript{60} recorded spontaneous auditory nerve activity from 10 cats pre- and post-salicylate administration using an incoherent spectral averaging technique, which allows the identification of continuous signals that have consistent frequency characteristics. It was noted that the results needed to be interpreted with caution because of the physiological stress salicylate places upon the animal. Marked changes in the spectral analysis of auditory nerve activity pre- and post-salicylate administration were reported, with a new peak of activity centred at or near 200 Hz being identified in all post-administration recordings. A higher-frequency, broader peak was also identified. Two animals in whom saline was administered did not demonstrate the new peaks of activity. Cazals \textit{et al}\textsuperscript{61} reported the effects of long-term salicylate administration in the guinea pig. Changes (specifically an immediate decrease followed by a progressive increase) in spontaneous activity recorded from the round window predated changes in hearing sensitivity, which the authors felt was an indication of high-frequency salicylate-induced tinnitus as this would be expected in humans under such conditions. Martin\textsuperscript{56} described spectral average recordings from the cochlear nerve of 14 human adult patients undergoing cerebellopontine angle surgery. In 12 patients with tinnitus, a prominent peak in the spectral average near 200 Hz was reported (see Fig. 2). Further animal studies report that ESNA is influenced by contralateral acoustic stimulation\textsuperscript{62}.

The origin of peaks within the spectrum of spontaneous neural activity recorded from guinea pigs undergoing salicylate administration was explored by McMahan and Patuzzi\textsuperscript{63}. They questioned the assumption of Cazals and Huang\textsuperscript{57} that the peaks are indicative of synchronous...
Two spectral peaks were identified. A peak at 170 Hz was thought to be consistent with the 200 Hz peak previously reported by Martin in humans (see Fig. 2). A spectral peak at 900 Hz was thought to arise from resonance of the primary afferent nerve membrane, with a potential contribution from neurones with similar membrane properties in the ventral cochlear nucleus. Evidence favouring the existence of these two peaks has also been reported by Searchfield et al. McMahon and Patuzzi suggested that the peaks of spontaneous activity recorded at 200 Hz and 900 Hz may in future be used to determine the location of physiological generators of tinnitus.

Medial efferent system involvement

Eggermont suggested that the efferent system might influence the perceived intensity of tinnitus, and associated annoyance, based on the observation that stressful situations may exacerbate tinnitus, and that...
techniques such as biofeedback may reduce tinnitus. In addition, the connection of the auditory efferent system with the reticular formation within the brain stem had been linked with the persistence of tinnitus as an alerting stimulus by Hazell and Jastreboff. Jastreboff and Hazell additionally suggested a role for the efferent system in modulating a cochlear mechanism of tinnitus generation.

Veuillet et al investigated the possibility that dysfunction of the medial efferent system was involved in tinnitus perception by measuring the suppressive effect of contralateral noise upon transient evoked otoacoustic emissions (TEOAE) in subjects with tinnitus localised to one ear only. The hypothesis that efferent dysfunction in the tinnitus ear would result in a smaller suppressive effect of noise upon TEOAE amplitude than in the non-tinnitus ear was only marginally supported. Large intersubject variability in the suppressive effect was noted.

Lind also measured the suppressive effect of contralateral broadband noise on TEOAE in 20 patients with unilateral tinnitus and symmetrical hearing, finding no significant difference between the suppression effect in tinnitus and non-tinnitus ears.

An alternative mechanism of efferent system involvement in tinnitus perception has been suggested by Robertson et al, following experimental evidence that, in the guinea pig, olivocochlear inputs to the cochlear nucleus can be excitatory, thus directly affecting ascending activity in the auditory pathway, separately from influence upon the cochlea. Efferent dysfunction might, therefore, be implicated in tinnitus perception generated at a brain stem level. However, a review of tinnitus experience following vestibular nerve section in humans, which involves ablation of the medial efferent pathway in the inferior vestibular nerve, indicated that total medial efferent dysfunction was not associated with troublesome or exacerbated tinnitus.

Somatic modulation

The modulation of tinnitus by somatosensory input was considered by Levine. Patients were first interviewed about their experiences of somatic modulation of their tinnitus, such as changes in pitch or intensity associated with face stroking or head movements. They were then asked to perform manoeuvres of a few seconds' duration to test for somatic effects, including teeth clenching, pressure on the occiput, forehead, vertex and temples, head turning and shoulder abductions. In the interview, 16 of 70 patients reported that they could somatically modulate their tinnitus (23%). On testing, however, 48 patients (68%) reported modulation of their tinnitus with at least one of the manoeuvres. The pattern of modulation reported was highly variable.
involving changes in intensity (both increase and decrease) and pitch. In all cases, these changes were transient. The results led Levine to conclude that 'somatic modulation appears to be a fundamental attribute of tinnitus', and to propose interactions between auditory perception and somatosensory input at the dorsal cochlear nucleus. Higher centres where such interaction also occurs (such as the SOC and IC) were not considered as somatically modifiable tinnitus is largely localised to one or other ear, and it was thought that binaural interactions in the SOC and higher centres would not have given rise to tinnitus heard to just one side. Levine\textsuperscript{71,72} also noted that cranial nerves V, VII, IX and X converge in the medullary somatosensory nuclei (MSN; Fig. 3) and that anatomical links between the MSN and the DCN had previously been described\textsuperscript{73}. The ability of some mammals to incorporate information about pinna position in sound localisation is indicative of such a pathway\textsuperscript{74}. Levine hypothesised that decreases in inhibitory MSN input to the DCN (specifically inhibition) might result in disinhibition of DCN activity leading to increased activity and the perception of tinnitus. Levine\textsuperscript{71} noted potential criticisms of this model. The DCN may not be the site of somatic and auditory interaction involved in tinnitus. The argument that the lateralisation of the tinnitus perception being evidence for the role of DCN somatic modulation of tinnitus is strong, but a role of the extralemniscal pathway in interactions between somatic and auditory pathways, as proposed by Moller et al\textsuperscript{75}, is also worthy of consideration and would allow unilateral tinnitus.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{schematic_diagram.png}
\caption{Schematic diagram of suggested interaction between somatic and otic pathways (following Levine\textsuperscript{72} with permission).}
\end{figure}
perception. Another potential criticism is that, whilst the anatomical
links between the MSN and DCN have been identified in the cat, the
situation is humans is less clear, and in particular no pathway from the
cunate/spiral tract of cranial nerve V to the DCN has been identified.

Analogies with pain

Analogy with chronic pain

Analogy between pain and tinnitus have been made many times in the
literature (see House & Brackmann76 and Evans77 for early examples). It
has been noted that: (i) pain, like tinnitus, can arise from a great variety
of lesions; (ii) there is no one specific mechanism for pain perception; (iii) pain
is a subjective phenomenon that is difficult to quantify; and (iv) treatment
of pain symptoms is difficult and often ineffective79,80. More specifically,
Moller1,80,81 considered the analogy between tinnitus and chronic pain in
terms of peripheral generation and of central persistence once the acute
injury has resolved. Whilst chronic pain is often a consequence of
peripheral injury, that injury may not in itself account for the sustained
nature of chronic pain. Moller81 considered that the involvement of the
CNS in such sustained perception was indicated by the relevant literature
(see Basbaum & Jessell82 for a comprehensive review). Such involvement
implies plasticity within the CNS. Similarly, while tinnitus is often
associated with peripheral auditory dysfunction, that dysfunction may not
account for the sustained and distressing tinnitus perception. Emotional
and environmental influences upon pain perception have been noted82. The
consequent large variation between individual experience of pain, makes
the development of effective therapy very difficult.

Cortical re-organisation, tinnitus, and analogies with phantom pain

The possible analogy between tinnitus and phantom limb pain was first
drawn by Goodhill in 195083. The concept that cortical re-organisation
similar to that involved in phantom limb pain84 might occur in auditory
cortical areas following change in the auditory periphery was first
reviewed in detail by Meikle85 and more recently by Salvi et al86. The
precise tonotopy that has been demonstrated in the central auditory
pathways means that de-afferentation of a specific portion of the
cochlea will, in the short-term, lead to reduced activity in the cortical
area with corresponding characteristic frequency (CF). If similar
measurements are made some months later, that area is again responsive
to sound, but many neurones now have CFs adjacent to that of the
lesioned region\textsuperscript{86}. This phenomenon has been demonstrated in animals\textsuperscript{87,88} (one study in particular reported that even a modest noise induced hearing loss resulted in significant cortical re-organisation\textsuperscript{89}) and in humans\textsuperscript{90,91}. One consequence of this re-organisation is that a disproportionately large number of neurones will be sensitive to frequencies at the upper and lower borders of the hearing loss. Salvi et al\textsuperscript{86} proposed that spontaneous activity in these areas might be perceived as tinnitus. Meikle\textsuperscript{85} suggested that the mechanism of such re-organisation might be the disinhibition of previously weak synaptic connections, and that the area of re-organisation might be limited to 1–2 mm, leading her to suggest that cortical re-organisation effects larger than this might represent re-organisation at a lower level in the auditory pathway where the tonotopic maps are smaller (the inferior colliculus for example). Re-organisation of the tonotopic map in the IC of the chinchilla following a high-frequency cochlear lesion has been demonstrated\textsuperscript{92}.

Evidence for re-organisation of the auditory cortex being a mechanism of tinnitus generation in humans was reported by Mulnickel et al\textsuperscript{93} and Dietrich et al\textsuperscript{91}. Whilst these studies involve small numbers of subjects, there are early indications that the identification of tinnitus mechanisms involving re-organisation and plasticity within the central auditory system may facilitate the development of novel pharmacological therapies for tinnitus\textsuperscript{60,94}.

The future

This review indicates that there are many potential mechanisms for tinnitus, and so the population of people with troublesome tinnitus will be heterogeneous in aetiology and experience, as is observed in clinical practice. It is envisaged that the objective of tinnitus mechanism research in coming years will be to determine the validity and relevance of the hypotheses regarding tinnitus generation to the clinical population, and to use that evidence to design effective clinical treatments.

Key points for clinical practice

- There are multiple potential mechanisms of tinnitus, and this accounts for the heterogeneity evident in the clinical population.
- The development of new and effective treatments will be greatly facilitated by identification of mechanisms in humans.
- The analogy between tinnitus and phantom limb pain, and the possibility of a role for 5-HT dysfunction in tinnitus, indicate the possibility of effective clinical intervention in tinnitus where these mechanisms are evident.
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