Tinnitus: neurobiological substrates

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Tinnitus is an auditory phantom sensation of ringing in the ears that is experienced when no external sound is present. It is a prevalent disorder that is frequently caused by insults to the peripheral auditory and somatosensory systems, especially in the elderly. This creates an imbalance between inhibitory and excitatory transmitter actions in the midbrain, auditory cortex and brainstem (where neural activity from somatosensory and auditory stimuli interact). This imbalance causes hyperexcitability often leading to the perception of phantom sounds. Although changes in transmitter–receptor systems have become better documented, there are currently no proven drug treatments for humans. Methods for preventing tinnitus have been demonstrated in animal studies.

Tinnitus is the general term for sound sensations (roaring, hissing or ringing in the ears) that cannot be attributed to an external sound source. Tinnitus that can be attributed to an internal sound source, such as a pulsating blood vessel, is called objective tinnitus and can generally be ameliorated surgically. Here I will only consider subjective tinnitus, which is a phantom sound sensation [1] often accompanying hearing loss and head and neck injuries or manifesting itself as a hypersensitivity to various drugs (Table I). Tinnitus is more common in the elderly but can also occur in children. It could become more common in the future as a direct consequence of the rise in recreational-noise-induced hearing loss (i.e. from overly loud music) combined with an increased life span.

Animal models

The neural substrate of tinnitus can only be adequately studied in animal models that show evidence of tinnitus under similar conditions to humans. Behavioral test models have been devised for rats [1–3], hamsters [4] and mice [5]. The findings have been taken as evidence that conditions that cause tinnitus in humans and these particular animal models will also cause tinnitus in other experimental animals, such as chinchillas, guinea pigs and cats. In cats, rats, mice and hamsters, changes in spontaneous neural activity in auditory nerve fibers (ANFs), the dorsal cochlear nucleus (DCN), the inferior colliculus (IC) and the auditory cortex have been recorded following the application of a tinnitus-inducing agent.

Tinnitus-inducing agents include excessively loud noise, salicylates, quinine, aminoglycoside antibiotics and cisplatin. In general, the spontaneous firing rates (SFRs) in ANFs decrease or stay the same after administration of these agents [6–9], although a near-toxic dose of salicylate has been shown to cause increased spontaneous firing rates in ANFs [10]. Contrasting with this reduced firing in the auditory periphery is the general finding of increased spontaneous activity in central auditory system structures after noise trauma or low doses of ototoxic drugs.

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TABLE 1

Epidemiology of tinnitus[a]

Number of subjects	1630
Traumatic[b]	
Noise (long duration or transient)	23.6%
Head and Neck Injury including whiplash	17.7%
Medical	
Otologic	13.8%
Drugs, medication	3.4%
Unknown	27.7%
Other	13.8%

[a]Data from the Tinnitus Archive, second edition, Oregon Health and Science University (www.tinnitusarchive.org).

[b]Factors as reported in questionnaires by tinnitus sufferers interviewed between December 1981 and August 1994.

These structures include the DCN [11–15], the external nucleus of the inferior colliculus (ICx) [16,17] and the secondary auditory cortex (AII) for salicylate and quinine [18], and the primary auditory cortex (AI) for noise trauma [19,20]. However, in the central nucleus of the inferior colliculus (ICc) in mice, no changes in SFR were found months after chronic salicylate administration or noise trauma [21]. Figure 1a shows the various findings superimposed on a simplified wiring diagram of the auditory nervous system. These findings of increased SFR have been attributed to reduced levels of central inhibition [probably γ-aminobutyric acid-(GABA)-ergic] in central auditory structures [2,22,23] leading to neural hyperactivity in IC [24].

In contrast to the lack of change in SFR [21], strong c-Fos immunostaining has been found in the ICc of rats, with little in the DCN and none in the ventral cochlear nucleus (VCN) after five days of chronic application of salicylate [25]. However, after one large dose of salicylate very little c-Fos- or arg3.1-related activity was found in the IC, whereas elevated levels were evident in auditory cortex and amygdala [26].

The findings cited above potentially support the previously proposed contribution of the extralemniscal pathway (DCN, ICx and AII) in acute salicylate- and quinine-induced tinnitus [27]. This is somewhat different from noise-induced tinnitus, which shows a nearly immediate, [20] as well as long-term [19], increase in the spontaneous firing rate in primary auditory cortex (AI) but not in ICc [21]. Presumably, the changes in SFR might originate in the AI, propagate to the AII and then centrifugally affect the ICx and DCN. Clearly, more studies are needed to address this issue.

Transient and chronic tinnitus

It is likely that there are different causes for immediate and long-term changes in SFR after the application of tinnitus-inducing agents. Most drug studies cited above have been acute and neural changes have been recorded within a few hours after drug application. These studies could have overlooked certain effects that only manifest after chronic sound or drug application and slow induction of tinnitus-like phenomena. Although large one-time doses of salicylate will cause transient tinnitus in humans, chronic use of low therapeutic doses of salicylate (e.g. in rheumatic arthritis) will cause tinnitus only in the long run, which is typically reversible and does not inevitably lead to hearing loss. Notable studies that explored the long-term effects of salicylate application in guinea pigs using the average frequency-spectrum of round-window electric noise (known to be generated by ANF spiking activity [28]) showed that the spectrum level went down in the first few days after the start of the application, in agreement with SFR results. However, in the course of the first few weeks of application, the spectrum level increases substantially without changes in the hearing threshold. This change in spectrum level, particularly manifested at frequencies around 1 kHz, has been credited to increased synchronization of nerve fibers spiking. An alternative explanation is an enhanced subthreshold resonance in the ANF dendrites that is caused by the activation of voltage-controlled Na^+ channels [29]. A consequence of this resonance might be an increased probability of doublet-spike firing, as observed following noise trauma in cat ANF [9].

Peripheral cause, central effect

In the AI, SFR recordings have been made from the same neurons before and up to six hours after noise exposure. The immediate effects of a one-hour exposure to very loud pure tones were an increase in threshold for the characteristic frequency range above the tone frequency but without an immediate change in SFR. However, after approximately two hours after exposure, SFR had increased significantly whereas response-threshold values improved to ~25 dB above pre-exposure levels [20]. Several weeks after the exposure, hearing losses had typically recovered further but SFR remained increased [30], even in regions where no significant hearing loss could be measured [19].

A notable finding was the increased synchrony in the spike firing by neurons immediately after the trauma [20], which increased in the following hours. This neural synchrony decreased after several weeks to slightly, but still significantly, elevated levels compared to controls [19]. A similar increase in spike-firing synchrony was found 45 min to 2 h after quinine administration [31]. It is not clear at present if the increased spike-firing synchrony has a causal relationship with tinnitus but in the cases cited it was always a consistent firing even without concomitant increases in SFR.

It is intriguing that in the DCN the increase in SFR only became significant 2–3 days after exposure to 140 dB sound pressure level (SPL) noise [12]. This could indicate that these changes are truly plastic and result from a homeostatic adjustment to a reduced drive from the auditory periphery, whereas the more immediate effects in the cortex could be caused by a fast downregulation of

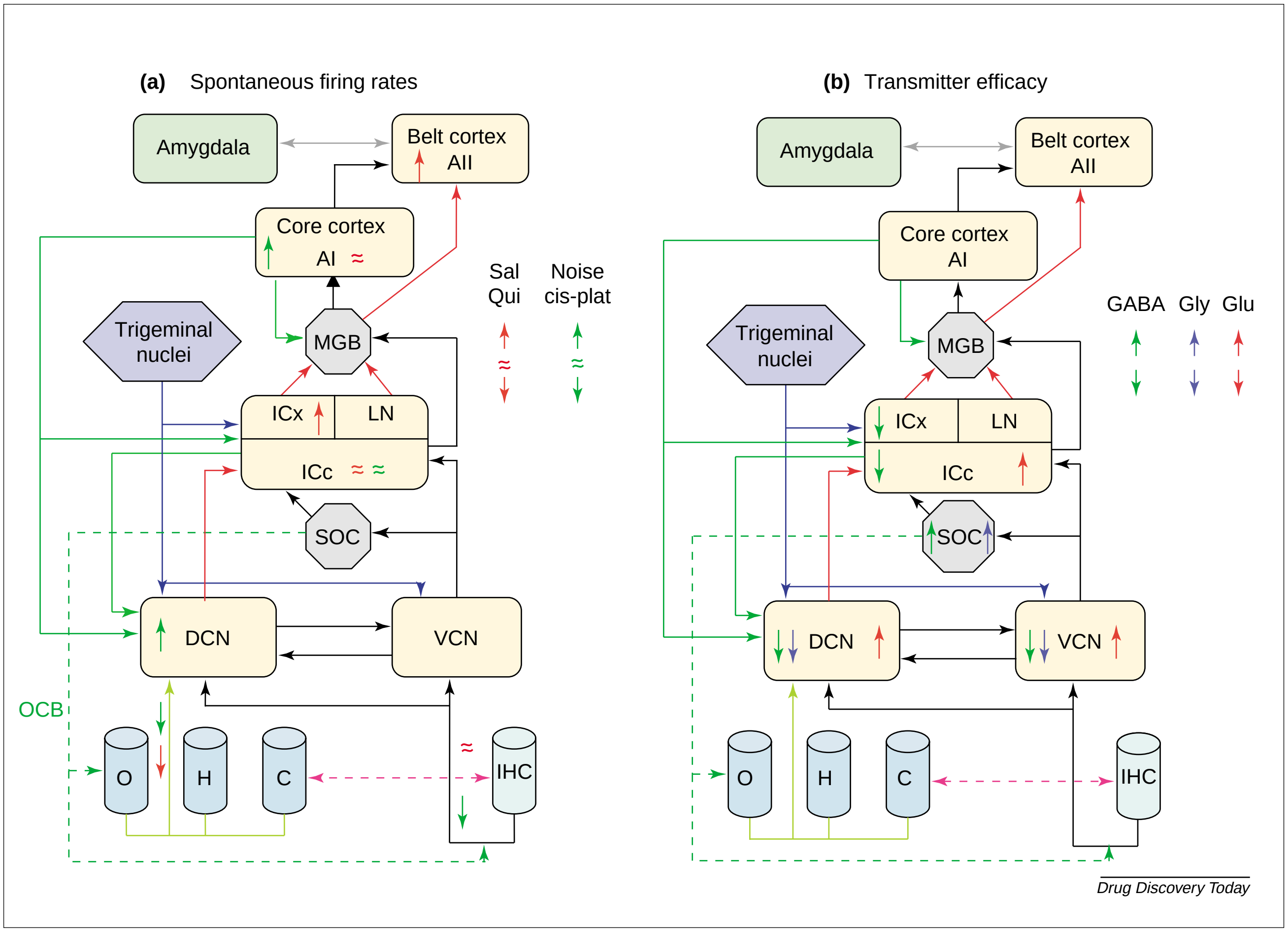

FIGURE 1

Schematic outline of the auditory system with tinnitus-related changes. The outline excludes binaural pathways and interhemispheric connections, and only shows major connections. Sound activates the outer (OHC) and inner (IHC) hair cells in the cochlea, here shown at the bottom of the figure. The cochlear action is to decompose multi-frequency signals into a spatial output organized according to frequency; this is called a tonotopic mapping. The OHC are mainly acting as amplifiers of the mechanical movement of the basilar membrane, thereby sharpening the frequency resolution and enhancing sensitivity. Their working point and effectiveness is under control of the central auditory system (CAS) through olivo-cochlear bundle (OCB) feedback (dashed green lines) from the superior olivary complex (SOC). The IHCs are the mechano-electric transducers (microphones) in the cochlea the neural output of which forms the auditory nerve. The auditory nerve fibers bifurcate to send collaterals into the ventral cochlear nucleus (VCN) and the dorsal cochlear nucleus (DCN): both structures show tonotopic maps. Tonotopic mappings are found throughout the CAS and the nerve fiber tracts that propagate this frequency specific information by the lemniscal pathway, which is indicated in the figure by black lines. The DCN in addition to receiving auditory nerve input also is innervated by fibers from various parts of the somato-sensory system (here indicated in blue color) so this structure is a multi-modal processing station that is likely heavily involved in tinnitus resulting from somatosensory insults. Because of its multi-modal character, this structure can be considered part of the extra-lemniscal pathway (indicated with red lines). Other parts of the extralemniscal pathway are the lateral nucleus (LN) and the external nucleus (ICx) of the inferior colliculus, parts of the medial geniculate body (MGB) in the thalamus and the secondary auditory cortex (AII), which are all characterized by sensitivity to somatosensory stimuli. Some auditory cortical areas project to the amygdala (top left in the figure) associated with fear conditioning and emotional processing and showing enhanced activity after salicylate. Strong direct feedback connections (shown here in green) exist between primary auditory cortex (AI) and DCN as well as from auditory cortical areas (not shown) via the central nucleus of the inferior colliculus (ICc). Thus, changes in cortical activity as a result of a loss of inhibition could change the subcortical activity in the ICc and in the DCN (direct) and even the cochlea (indirect via the olivo-cochlear bundle). Changes in the DCN, in turn, will directly affect the processing of lemniscal activity at the level of the VCN and the ICc. Thus there may be a synergy between changes occurring in the cortex and those in the brainstem. In **(a)** the changes in SFR are shown for salicylate and quinine (red arrows) and noise trauma and cisplatin ototoxicity (green arrows). In **(b)** the common effects of the various ways to induce tinnitus and cochlear ablation on the efficacy of glutamate (Glu), GABA and Glycine (Gly) in various structures are shown. The changes are again indicated by colored arrows (see insert for code).

GABAergic activity. It is also possible that corticofugal activity has a role in the gradual changes observed in the DCN [32].

After long-term administration of cisplatin [12] it was found that, as long as the outer hair cells (OHCs) were intact, there was no increase in spontaneous activity in the DCN. In cases of severe damage of the OHCs, the spontaneous activity in the DCN increased, but less so if the inner hair cells (IHCs) were also damaged. This led to the hypothesis, as suggested previously [33], that tinnitus only arises after selective damage of the OHCs and putatively by a loss of activation of the granule cells in the DCN by type II ANFs that innervate the OHC. This in turn would lead to reduced activation of the cartwheel and stellate cells and thereby in a disinhibition of the fusiform cells, which form the output of the DCN to the IC.

The findings of Cazals *et al.*, [28] showing that the noise spectrum recorded from the round window during chronic salicylate treatment changes only after several days, also opens the possibility that the late changes in the DCN after noise trauma [12] are caused by slow increases in the spontaneous activity (or burst-firing) in ANFs. The increased SFR in the DCN must ultimately become independent of ANF input because subsequent sectioning of the auditory nerve had no effect on the SFR in the DCN [34].

Because most salicylate studies have been acute (i.e. recordings were made within a few hours after administration), the findings of an unchanged SFR in the ANFs [6,7] and increased SFR in the ICx [15–17] can not rule out a peripheral component for tinnitus caused by chronic salicylate treatment [3,28]. However, the effects of noise trauma on ANFs were all investigated after the establishment of the permanent threshold shift, so the decrease of spontaneous activity in these ANFs, combined with increases in the AI, requires a central source of the ensuing tinnitus. This source is probably not the ICc [21].

Causes of tinnitus might be multisensory

The second largest cause of tinnitus (after insults to the cochlea) is putative abnormal activity in the somatosensory system [35–37] resulting from head and neck injuries, whiplash and various mandibular and dental problems [38]. Nerve fibers from the trigeminal ganglion, dorsal column nuclei and trigeminal nuclei innervate the CN, superior olivary complex (SOC) and IC. The ophthalmic and mandibular divisions of the trigeminal ganglion innervate the magnocellular and granular regions of the VCN, respectively. In addition, the cuneate nucleus forms the source of the mossy fibers in the DCN. The mandibular division is partly in the middle-ear reflex circuit. The trigeminal circuit is also part of the olivocochlear feedback loop. In combination, the interaction of the somatosensory systems with the auditory system provides for powerful feedback loops that regulate peripheral sensitivity (Figure 1a).

The DCN is an important integration site for auditory and somatosensory information (e.g. from the pinnae [39]) but influences of trigeminal nerve activity are also evident in the VCN [40]. Imbalances between the auditory and somatosensory input can lead to imbalances between excitation and inhibition, either by reduced auditory input (as caused by noise trauma) [13,14] or, putatively, after increased somatosensory input following injury or inflammation.

A role for calcium

Intracellular Ca^{2+} has a role in regulating the balance between inward and outward currents in neurons and hair cells. The function of the hair cells also depends on the Ca^{2+} signaling pathways governing the fast neurotransmitter exocytosis of IHCs and the slow motility changes of the OHCs. There is increasing evidence of a role for Ca^{2+} in the fast transduction process in hair cells [41]. The effects of noise, salicylate and quinine include a sustained increase in the Ca^{2+} concentration in hair cells [42]. Salicylates also cause a dose-dependent decrease in the free perilymphatic Ca^{2+} concentration [43]. Decreasing the extracellular Ca^{2+} concentration [44] can result in burst-firing behavior in neurons. Increased burst-firing was observed after salicylate application in ICx [16] but not in ICc [21]. During noise exposure, there is a very large transient increase in the endolymph Ca^{2+} concentration, similar to the sustained Ca^{2+} increase observed in animals with experimentally induced endolymphatic hydrops (the animal model for Ménière's disease) [45]. Tinnitus, sustained as well as transient, is one of the defining characteristics of Ménière's disease.

Glutamate neurotoxicity

Excess glutamate, kainate and α-amino-3-hydroxy-5-methyl-4-isoxalone propinoic acid (AMPA) all cause ANF dendrite swelling followed by membrane disruption, whereas *N*-methyl-D-aspartate (NMDA) application does not. Continuous release of glutamate from intact IHCs induces growth of new dendritic processes after noise trauma damage [46]. This regrowth is probably the cause of a reduction in noise-induced hearing loss following recovery in an enriched acoustic environment compared with recovery in a quiet environment [20]. Guitton *et al.* [3,47] suggest that salicylate-induced tinnitus results from inhibition of cyclooxygenase activity resulting in altered arachidonic acid metabolism, which potentiates NMDA-receptor currents in the cochlea. The increased opening probability of NMDA receptors can result in burst or epileptiform firing activity in ANFs, potentially leading to tinnitus. Such bursting activity has been found in some ANFs after noise trauma [9].

Glycine and GABA downregulation and glutamate strengthening

Noise exposure lowers GABA-mediated inhibition in the IC [48]. Glutamic acid decarboxylase (GAD) levels in the IC increased immediately after noise exposure but returned to lower than control values 30 days after exposure [22]. Because GAD is the rate-limiting enzyme in the formation of GABA, an increase in GAD concentration suggests an initial upregulation of the reservoir pool of GABA after the trauma (probably as a compensatory mechanism) but a downregulation later. In the first week after exposure to unilateral noise trauma [49], electrically evoked glutamatergic transmission in the ipsilateral VCN slice increased, whereas its uptake was depressed. In the DCN, glutamate-release was increased and uptake was unchanged. At 14 days after exposure, glutamatergic release and uptake were lowered, probably because of the degeneration of ANFs. At 90 days after exposure, glutamatergic release and

AMPA-receptor binding were sharply increased. This was understood to be caused by neuro-plastic mechanisms similar to those observed after unilateral cochlear ablation. The findings are consistent with a noise-induced strengthening of glutamatergic transmission in VCN and DCN leading to hyperexcitability in the auditory pathways [24]. Surprisingly, spontaneous glutamate release measured by hyperfusion in slice was not affected by noise exposure.

After salicylate application, an upregulation of GAD and a decrease in $GABA_A$-receptor affinity was observed in the IC of rats showing behavioral evidence for tinnitus [2]. Interestingly, in aging animals, there was an upregulation in the number of $GABA_A$ receptors, probably to compensate the significant loss of presynaptic GABA release [50]. The reduced GABA release might explain the increasing incidence of tinnitus in the elderly who have suffered moderate noise-induced hearing loss earlier in life.

A more drastic alteration of cochlear output, compared with the usually partial noise- or drug-induced hearing loss, is found after unilateral removal of one cochlea. In that case, there occurs a downregulation of bilateral glycine release in DCN and a reduction in the number of glycine receptors in VCN and lateral superior olive (LSO), as well as a strengthening of glycinergic activity in the medial superior olive (MSO) [51,52]. In the IC, GABA uptake is downregulated and D-aspartate uptake is bilaterally upregulated [53]. The commonality of the effects is shown in Figure 1b.

Tinnitus reflects the nasty side of neural plasticity

Animal research, as reviewed above, has shown the response properties of neurons following ototoxic drugs and hearing injuries, and pointed to changes occurring in the balance of excitation and inhibition at multiple levels of the auditory pathway [2]. It is reasonable to assume that the effect of this change in balance in the central nervous system and the auditory cortex contributes in some way to tinnitus. One change that has been well documented is alteration of tonotopic maps in the AI after noise-induced cochlear damage (Figure 2). In the intact auditory cortex, there is an orderly representation of spectral frequency across the auditory cortex in a caudal-rostral direction; the tonotopic map reflects place-coding of sound frequency by the cochlea. After noise trauma, and probably also after other traumatic hearing losses, the tonotopic organization in the cortex is changed such that cortical neurons with characteristic frequencies (CFs) in the frequency region of the hearing loss no longer respond according to their place in the tonotopic map, but reflect instead the frequency tuning of their less affected neighbors (Figure 2b [20,30]). Neurons with CFs in the affected region also show increased spontaneous activity and increased neural synchrony [19,20]. These results point to a potential link between reorganization of the cortical tonotopic map, changes in neuron SFRs and tinnitus [32]. These changes in response properties of neurons, and changes in cortical tonotopic map organization, which are induced by noise exposure and other tinnitus-inducing agents, do not occur in isolation of one another. Decreases in intracortical inhibition and increases in SFRs after the loss of peripheral input to central neurons can promote the development of synchronous spiking activity [19,20] by prolonging postsynaptic depolarization and increasing the likelihood of temporally coincident inputs converging on synapses. In the normal central auditory system surround inhibition (the inhibition surrounding the excitatory part of the receptive field of a neuron) produced by thalamocortical input would be expected to restrict synchronous activity to neurons tuned to properties of the acoustic stimulus, thereby leading to normal auditory perception. However, when the constraints of intracortical inhibition are weakened, distributed synchronous spike-firing activity can develop [20] and stabilize over wider cortical territories, leading to the perception of sounds that are physically absent (tinnitus).

Chronic tinnitus and chronic pain display considerable similarities, including plastic changes in the central nervous system leading to hypersensitivity to sensory stimuli and a change in the way those stimuli are perceived. Involvement of the sympathetic nervous system has been postulated in chronic pain and tinnitus [54]. Tinnitus has been classified among the positive symptoms that arise after lesions of the nervous system [55], sharing with neurogenic pain the phenomenon of low-threshold calcium spike-burst firing in the medial thalamus. Another example of similarities in tinnitus and pain is that the vanilloid receptor type I (VR1) is expressed in the spiral ganglion of rats [56]. VR1 is commonly expressed in dorsal root and trigeminal ganglion cells and allows us to appreciate the painful effect of hot peppers. In case of an inflammatory response, arachidonic acid can be metabolized by lipooxygenase, and its metabolites act as agonists at the VR1-binding site. This could provide another mechanism for hyperacusis and tinnitus.

Prevention and treatment of tinnitus

Drug treatment of tinnitus in humans has been largely unsuccessful, although Xanax® (Pfizer) has been shown to reduce the loudness of tinnitus slightly [57], the only consistent (but short-lived) relief being that provided by lidocaine infusion. In an animal model [17], the effect of lidocaine on IC neurons that showed increased SFR after salicylate application was short-lived (~5 min) and did not affect all neurons similarly. Successful prevention of tinnitus in animal models includes: administration of an L-type Ca^{2+} channel blocker (nimodipine) that prevented quinine-induced tinnitus [58]; dietary supplements of $CaCl_2$ in drinking water three days before application of salicylate in guinea pigs [43]; application of NMDA antagonists in the cochlear perilymph of rats blocked the behavioral evidence of tinnitus after salicylate

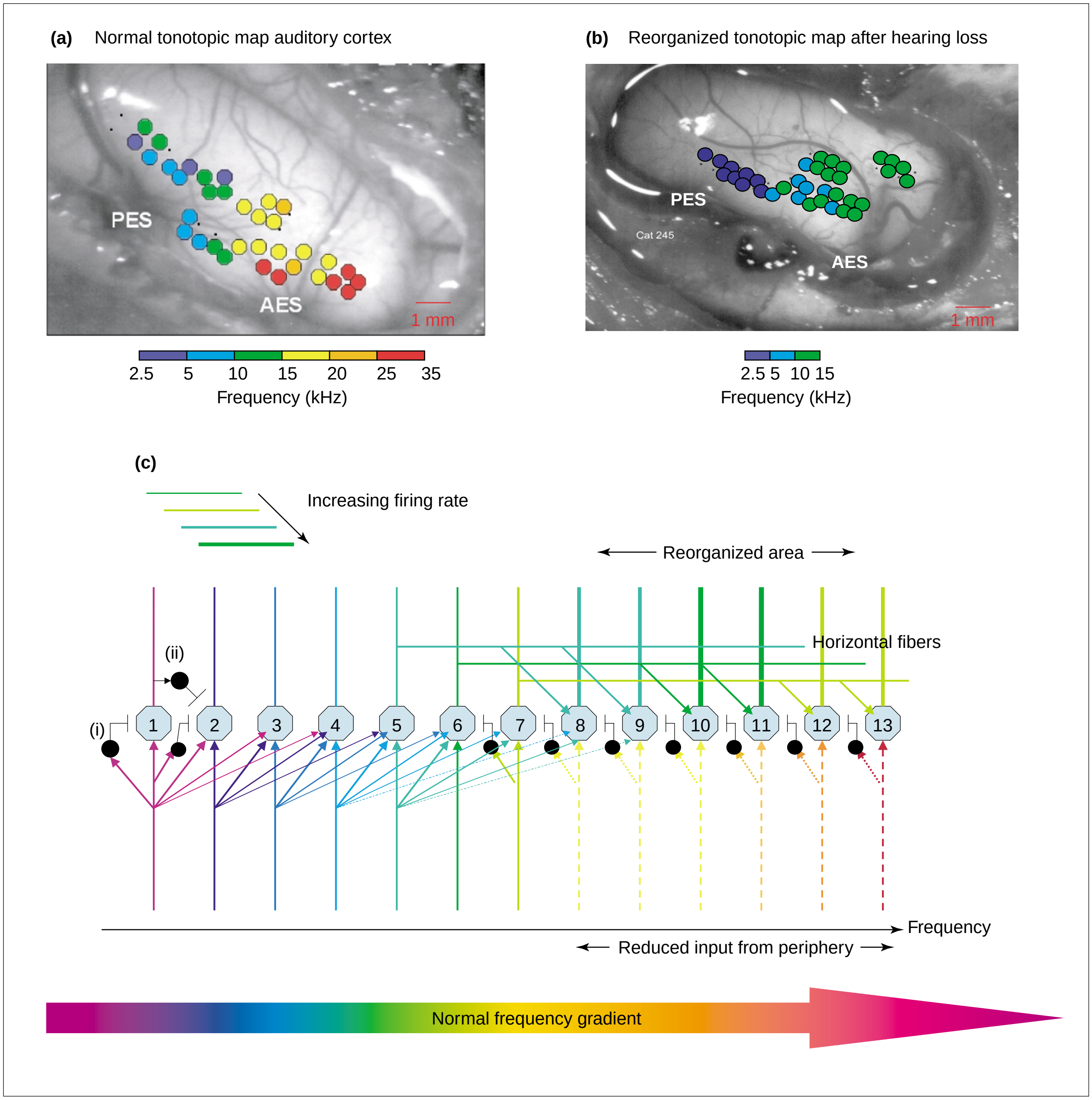

FIGURE 2

Normal and reorganized tonotopic maps in AI. The characteristic frequency at each recording site is color coded and overlaid on a photograph of the cortical surface for **(a)** a normal control cat and **(b)** a cat with a noise induced hearing loss. The hearing loss was limited to frequencies above 10 kHz and amounted to 3 dB at 12 kHz, 12 dB at 16 kHz, 22 dB at 24 kHz and 23 dB at 32 kHz. **(c)** Shows the effect of a restricted high frequency hearing loss on the input to some pyramidal cells (numbered 1–13) in auditory cortex. The arrow shows the normal frequency gradient of the inputs conveying the tonotopic mapping. The thin vertical lines leading to the cortical cells are color coded to reflect their frequency-specific input. For the higher frequencies, covering the range of the hearing loss, the lines are shown as dashed to indicate their reduced ability to activate cortical cells at low stimulus levels and during silence. Numerous divergent connections lead from each thalamic cell to a range of cortical cells (these are indicated by lines with the same color). A few inhibitory feed-forward connections are indicated **(i)**. These affect the same cells that receive their thalamic inputs. Feed-back inhibition **(ii)** is also prevalent but only shown for cell 1. The assumption is that loss of input not only limits the excitation but even more strongly the inhibitory feed-forward activity. As a result, the diverging thalamic inputs from neighboring, unaffected cells, and the inputs from cortical cells via horizontal fibers, face less competition from inhibition at those cortical cells deprived from thalamic input. As a result, these excitatory inputs are disinhibited or 'unmasked' and can impose their own frequency-selective inputs on the cortical cells in the hearing loss range which will ultimately result in reorganization of the tonotopic map in the hearing loss animal. Adapted, with permission, from [32].

application [3]; and post-trauma rearing of cats in an enriched acoustic environment that spectrally matches the inverse of the hearing loss region [59].

Implants and tinnitus

Cochlear implants can reduce tinnitus volume and awareness in 86–92% of patients and rarely (<10%) enhances it

[60,61]. Cochlear implants did slightly better than hearing aids in reducing tinnitus: 54% in cochlear implant patients versus 48% in hearing-aid users [62]. As yet, the mechanism of action remains unknown, but it probably provides a more balanced cross-frequency input to the brain, perhaps similar to that provided by an enriched acoustic environment [59].

Conclusions

Transient and long-standing tinnitus probably have different underlying mechanisms. Findings on acute tinnitus point to a neuroexcitotoxic effect that increases glutamatergic pathway activity, whereas long-standing tinnitus requires changes that include plastic as well as homeostatic mechanisms that resemble those of chronic pain. These mechanisms also cause changes, which have been linked to tinnitus, in the organization of the cortical place-frequency map. In transient and long-standing tinnitus, SFRs are increased in the auditory central nervous system. The non-lemniscal auditory system might have a key role in tinnitus generation because it is more sensitive to drug-induced tinnitus and provides a substrate for interaction between the auditory and somatosensory systems. Prevention of tinnitus in animal models shows promise, but drug treatment of long-standing tinnitus in humans has so far been unproven.

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