Chapter 30
The Pharmacologist

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Keypoints

1. One in 10 adults has subjective tinnitus, and for 1 in 100 adults, tinnitus severely affects their quality of life.
2. Despite the significant unmet clinical need for a safe and effective drug targeting tinnitus relief, there is currently not a single FDA-approved drug on the market.
3. Since in some individuals, tinnitus causes irritability, agitation, stress, depression, insomnia, and interferes with normal life, even a drug that produces a small but significant effect would have a huge therapeutic impact.
4. A glimpse of hope is appearing in the near future, as some pharmaceutical industries now have compounds targeting tinnitus in their pipeline.
5. If these compounds finally reach the market, they will set a new era that will revolutionize the treatment of tinnitus.

Keywords Tinnitus • Phantom sound • Animal models • Lead compounds • Drug discovery

Tinnitus: A Clinical Unmet Need

Despite the significant unmet clinical need for a safe and effective drug targeting tinnitus relief, there is currently not a single FDA-approved drug on the market. For the majority of tinnitus sufferers who seek medical advice, the treatment goals are aimed at symptomatic relief (i.e. reduce or eliminate the tinnitus that is referred to as inside the head and/or ears). Symptomatic treatment is usually justified, because serious underlying pathologies are rare (see Sect. 30.2). Over four million prescriptions are written each year for tinnitus relief in Europe and the US, but these are all off-label prescriptions from a wide variety of therapeutic drugs, many of which are associated with considerable side effects or are ineffective in relieving tinnitus. There is, therefore, a large need for an effective drug therapy targeted at tinnitus, with minimal side effects compared to current medications prescribed off-label. Since in some individuals, tinnitus causes irritability, agitation, stress, depression, insomnia, and interferes with normal life, even a drug that produces a small but significant effect would have a huge therapeutic impact. However, disappearance of tinnitus should be the ultimate goal.

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Tinnitus can be Pharmacologically Targeted

While the initial lesion might affect the peripheral organ of the auditory system, the neural correlate of the perceived sound is most likely in the central auditory circuitry [1] and there is growing evidence that changes in neuronal activity in different parts of the auditory pathway, including the dorsal cochlear nucleus, inferior colliculus, thalamus, and/or auditory cortex may be involved in tinnitus pathology [2–9]. Neuronal excitability can be modulated by different neurotransmitters, neuromodulators, and voltage-gated channel acting compounds [10–14], so there is no reason to believe that activity-driven changes underlying

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tinnitus cannot be pharmacologically targeted. The fact that a local anesthetic, the voltage-gated sodium channel blocker lidocaine [15], given intravenously, leads to the temporary disappearance of tinnitus or a major change in the nature of the tinnitus in 70% of patients [16–22], indicates that Pharmacologic agents can have beneficial effects on many forms of tinnitus.

Challenges Toward Developing a Tinnitus Drug

The quest for effective tinnitus therapies faces significant challenges. First, tinnitus is only a symptom that might be the manifest of different underlying pathologies. Differential diagnosis of triggering events and temporal onset should allow for a more rational and effective pharmacological approach. Therefore, the careful classification of tinnitus patients together with the search for drugs that can successfully target each underlying pathology becomes a priority. Moreover, the current limited understanding of the neural substrates of tinnitus, together with the lack of adequate animal models that can faithfully recapitulate its pathology, hampers the screen for new molecules in preclinical studies. Finally, because the first tinnitus drugs are yet to be approved, regulatory agencies such as the Food and Drug Administration (FDA) or the European Medicines Agency (EMEA) lack standardized protocols for their approval process. The often considerable placebo effect is another obstacle in selecting new substances for tinnitus treatment.

Many pharmacological agents have been used off-label to treat individuals with tinnitus. These include anticonvulsants, anxiolytic, antidepressants, NMDA antagonists, cholinergic antagonists, antihistamines, vasodilators, and antipsychotics, to name a few (see Chap. 78) [23, 24]. Some drugs have been reported to provide moderate relief of symptoms in a subset of patients. Careful clinical observations along with data from clinical trials have provided useful clues for deciding on a rational course of drug therapy for selected patients. However, most drugs have not proven sufficient effectiveness in randomized controlled clinical trials in order to be marketed specifically for tinnitus, highlighting the importance of selectively targeting the underlying pathological cause of tinnitus.

The first step toward designing a successful strategy in the search for tinnitus drugs would most likely include finding criteria by which to stratify tinnitus patients included in trials. As previously discussed, tinnitus often occurs as a result of insults to the ear, such as from noise exposure or administration of specific pharmacologic agents. It can also be caused by ear or head injuries, some diseases of the ear, and ear infections [1, 25]. In some cases, the causative agent remains unknown. Therefore, the identification of the triggering cause should aid in selecting the most adequate pharmacological approaches. In addition, tinnitus sounds can take a variety of forms, such as buzzing, ringing, whistling, hissing, or a range of other sounds. It can be a benign sound that is heard only occasionally or it can be devastating roars that occur 24 h a day, which prevent its sufferers from sleep or the ability to do intellectual work. All degrees of subjective tinnitus occur in between these extremes. Tinnitus is also often associated with other symptoms, such as hyperacusis and distortion of sounds [25]. Affective disorders, such as anxiety, phonophobia, and depression, often accompany severe tinnitus, and that form of tinnitus can lead to suicide. With such differences in etiology and symptoms, heterogeneity within tinnitus patients is expected. Thus, the tinnitus drug discovery endeavor faces the "one drug won´t fit all" situation. The fact that a subgroup of patients who have intermittent tinnitus that sounds like a typewriter, popcorn, or ear clicking receives significant benefit from carbamazepine [26, 27] indicates that "subtyping" tinnitus is highly needed for successful treatment. Efforts toward establishing subgroups of tinnitus are under way [28] and will most likely aid the selection of patients in future clinical trials.

An additional challenge in the design of drugs for the treatment of tinnitus derives from the fact that the neural substrates underlying tinnitus are far from being fully understood. An increase in spontaneous firing rates or neuronal synchrony in different parts of the auditory pathway as well as changes in cortical tonotopy have been proposed as potential correlates of tinnitus [1, 29]. Modern drug discovery is mostly centered on the identification of new lead molecules that interact with discrete molecular targets. This is a reductionistic approach that mainly focuses on sites of drug action. Although it has been useful in developing molecules such as statins (inhibitors of HMG CoA reductase) and HIV protease inhibitors [30], central nervous system

acting drugs owe their clinical effectiveness to actions at multiple molecular targets [31]. Thus, this reductionistic approach is most likely inadequate for a central nervous system disorder such as tinnitus.

Although a well-defined neuronal target would ease the path toward drug discovery, the empirical approach that has been used for most central nervous system disorders should not be precluded in the case of tinnitus. The importance of this approach in central nervous system drug discovery can be appreciated in the case of morphine and barbiturates, whose mechanisms of action were unknown when these drugs were introduced for human use [30]. In fact, most central nervous system acting drugs were discovered serendipitously. Thus, for example, valproic acid was used as an organic solvent in research laboratories for eight decades, until the observation of action against pentylenetetrazol-induced convulsions in rodents was made [32]; chlorpromazine was used to enhance recovery from surgical anesthesia before it was found to alleviate some symptoms of schizophrenia [33]; gabapentin was first developed as an anticonvulsant and is now used for treating neuropathic pain [34]. Thus, following these past experiences with central nervous system acting drugs, the search for drugs to alleviate tinnitus should not wait until the neural correlates are identified.

Before a compound is judged suitable for testing in humans, it must first demonstrate safety and efficacy in animal models. A drawback in the development of a tinnitus drug is the lack of validated animal models in which to test or screen for compounds. The basic dilemma faced by the animal researcher who wants to study tinnitus is whether or not the animals have the disorder. The experimenter has to find a way by which a rodent tells him about the ringing in its head. Several animal models are being developed, which are based either on noise exposure or on the administration of salicylate (see Chap. 16 and [35–37]). An additional challenge is imposed by the fact that, in humans, tinnitus is accompanied by the activation of a distress network that involves the limbic system [38–40]. This is probably not recapitulated in the animal models. However, animal models that have been developed for complex central nervous diseases such as depression or schizophrenia do not completely recapitulate the disease itself. Moreover, they are only of limited value for predicting treatment efficacy in humans [41]. However, in spite of all these drawbacks, these animal models have proven useful. In addition, in psychiatric diseases, empiric pharmacology has driven science. Thus, the serendipitous observation that central nervous system acting drugs like chlorpromazine calmed inmates of a psychiatric asylum has given way to the dopamine theory of schizophrenia and to the serotonin theory of depression and anxiety [41, 42]. These theories remain the pillars of the animal models used for preclinical validation, in spite of the fact that there is more to the major psychoses than alterations in these two neurotransmitter systems. Thus, the search for drugs to treat tinnitus should not wait for the refinement of the animal models. Moreover, the identification of compounds that alleviate tinnitus would not only lead to a better treatment but would also serve as a possible starting point for the understanding of the neural correlates of this condition, and thereof for the generation of better animal models, which target these neural substrates.

Finally, since no drug having tinnitus as its primary indication has been approved so far, there are no standardized protocols for the approval of a tinnitus drug by regulatory agencies like the FDA and EMEA. Therefore, the first pharmaceutical industry to develop a tinnitus drug will have to pave the way. In addition, tinnitus being a subjective phenomenon, assessment of outcome is probably the single most important factor in conducting a clinical trial. Widespread recognition that consistency between research centers in the ways that patients with tinnitus are assessed and how outcomes following interventions are measured would facilitate more effective co-operation and more meaningful evaluations. At the first Tinnitus Research Initiative meeting held in Regensburg in July 2006, which gathered worldwide tinnitus experts, an attempt was made to establish a consensus both for patient assessments and for outcome measurements [43].

Tinnitus and the Pharmaceutical Industry

Pharmaceutical companies are aware of the fact that there is a large market for a drug indicated for tinnitus relief. Evidence for this exists in the scores of patents that have been filed worldwide on potential drugs that may offer relief. Furthermore, tinnitus can be found attached to long lists of indications in many more patents filed on molecules aimed at a range of diverse

therapeutic classes. As indicated above, in spite of the fact that there is a significant unmet clinical need for a safe and effective drug targeting tinnitus relief, there is no FDA-approved drug currently on the market. The Royal National Institute for Deaf People, in the UK, estimates that a novel tinnitus drug could have a product value of US $689 million in its first year of launch [44]. However, there are very few pharmaceutical and/or biotechnology companies with tinnitus compounds in their R&D pipeline. A search carried out in the investigational drug databases Pharmaprojects (http://www.pharmaprojects.com), AdisInsight (http://www.adisinsight.com), Prous DDR (http://www.prous.com), and IDdb3 (http://science.thomsonreuters.com) shows that the following companies are developing a compound for tinnitus: Epicept, a lidocaine patch at phase II; Sound Pharmaceuticals, ebselen, a glutathione peroxidase mimetic and inducer at phase II; Auris Medical, AM101, an NMDA receptor antagonist, at phase II; Ipsen, a ginkgo biloba extract, at phase I; Merz, neramexane, an NMDA antagonist and an α9 α10 nicotinic cholinergic receptor blocker [45], at phase III; and GSK, vestipitant, a neurokinin 1 receptor antagonist [46], at phase II.

From the above, it can be concluded that there are a few companies with tinnitus compounds in their pipelines in spite of the existence of such a huge market for this clinically unmet need. This most likely derives from the existing challenges described in the previous section. The lack of serendipitous discoveries of effective treatments for tinnitus has severely limited insight into disease pathology, which is often gained by such fortuitous pharmacological findings. It is the absence of a fully determined mechanism for tinnitus that makes research into this area potentially very high risk. However, if any of the above compounds reaches the market, they will set a turning point both in the treatment of tinnitus as well as in the development of future compounds.

Potential Pharmacological Targets

The search for drugs that target tinnitus is hampered by the lack of a deep knowledge of the underlying neural substrates of this pathology. Initially considered an inner ear pathology, it is now clear that at least chronic tinnitus is a central nervous system disorder. As indicated above, changes in cortical tonotopy, as well as increase in spontaneous firing rates and neuronal synchrony in different parts of the auditory pathway, have been proposed as potential correlates of tinnitus [1, 29].

After noise trauma induced hearing loss, one of the main causes leading to tinnitus, changes in tonotopic organization in the cortex are observed. Cortical neurons with characteristic frequencies 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 [47–49]. Magnetic source imaging studies confirm this reorganization in human patients [50]. This suggests that reorganization of the cortical tonotopic map and tinnitus are correlated. Interestingly, providing an acoustically enriched environment spectrally matching the hearing loss prevents this reorganization [51, 52]. Thus, preventing neuronal reorganization by an acoustically rich environment might become a treatment strategy to prevent the establishment of the long-term plastic changes that follow exposure to noise trauma. However, most clinicians are faced with the problem of treating tinnitus patients when tinnitus is most likely a chronic condition in which tonotopic rearrangements along the auditory pathway are already established. Can established tonotopic rearrangements in the auditory cortex be reversed? Experiments in laboratory animals that combine sound exposure with electric stimulation of certain neuronal pathways/circuits show promising results. In the primary auditory cortex, dopamine release has been observed during auditory learning that remodels the sound frequency representations [53]. The stimulation of dopaminergic neurons in the ventral tegmental area of rats, together with an auditory stimulus of a particular tone, increases the cortical area and selectivity of the neural responses to that sound stimulus in the primary auditory cortex while it decreases the representations of nearby sound frequencies [54]. In addition, episodic electrical stimulation of the nucleus basalis of rats, paired with an auditory stimulus, results in a massive progressive reorganization of the primary auditory cortex in the adult rat. Receptive field sizes can be narrowed, broadened, or left unaltered depending on specific parameters of the acoustic stimulus paired with nucleus basalis activation [55]. The nucleus basalis contains both cholinergic and gabaergic neurons [56, 57]. Thus, taken together, these results indicate that sound therapy coupled with drugs that can modulate the neurotransmission of the

pathways/circuits involved in the described plastic events would be an interesting avenue to investigate.

Additional neural correlates of tinnitus include neuronal spontaneous hyperactivity in the reorganized region and increased neural synchrony [48, 52, 58]. Neuronal hyperactivity can be modulated by many multiple drugs that target either voltage-gated ion channels or neurotransmitter receptors. However, examples of such drugs like benzodiazepines, anticonvulsants, NMDA antagonists, and calcium antagonists, although effective in some patients, have not proven effective in double-blind placebo-controlled clinical trials [23]. Recently, in a preliminary report using a rat behavioral model, the potassium channel modulator Maxipost (BMS-204352) reduced behavioral evidence of salicylate-induced tinnitus in a dose-dependent manner [59]. This compound is a KCa1.1 (BK) and a Kv7 positive modulator [60, 61]. Since potassium ion channels play an important role in regulating the resting potential and spontaneous and evoked neural activity, potassium channel modulators represent potential important compounds for tinnitus therapy.

The above are only some few challenging ideas concerning ways to revert altered neuronal activity, synchrony, and tonotopy observed in the auditory pathway in tinnitus. However, it is a reductionistic approach, since it only takes into account changes observed in the auditory pathway. As has been shown in the somatosensory system, auditory cortex activation is essential, but probably not sufficient for auditory conscious perception [62, 63]. Moreover, for most patients, tinnitus is more than mere changes in the auditory pathway and implicates the activation of a distress network [38–40]. This brings us back to the notion that central nervous system acting drugs, in particular, owe their clinical utility to actions at multiple molecular targets [31]. This is most likely the scenario we are facing in the search of a drug to alleviate tinnitus.

The Time is Right

For many years, the standard of care for dealing with tinnitus patients has been, "You need to learn to live with it." Although we are far away from fully understanding tinnitus, the chances for a solution are much brighter than they were a decade ago. The development of behavioral measures of tinnitus in animals combined with physiological, biochemical, molecular, and imaging techniques are likely to provide important insights into the underlying causes of tinnitus. Tinnitus animal models will provide a way to screen for drugs that can suppress the disorder. The potential market for an FDA-approved drug to treat tinnitus is huge. Several existing drugs have been reported to provide significant relief from tinnitus in subsets of patients. Looking toward an exciting future, patients and clinicians may finally receive encouraging news if the compounds under development by several pharmaceutical industries finally reach the market. If they do, they will set a new era that will revolutionize the treatment of tinnitus.

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References

1. Eggermont JJ (2007) Pathophysiology of tinnitus. Prog Brain Res 166:19–35.
2. Eggermont JJ (2008) Role of auditory cortex in noise- and drug-induced tinnitus. Am J Audiol 17:S162–9.
3. Kaltenbach JA and DA Godfrey (2008) Dorsal cochlear nucleus hyperactivity and tinnitus: are they related? Am J Audiol 17:S148–61.
4. Bauer CA, JG Turner, DM Caspary et al (2008) Tinnitus and inferior colliculus activity in chinchillas related to three distinct patterns of cochlear trauma. J Neurosci Res 86:2564–78.
5. Lanting CP, E De Kleine, H Bartels et al (2008) Functional imaging of unilateral tinnitus using fMRI. Acta Otolaryngol 128:415–21.
6. Reyes SA, RJ Salvi, RF Burkard et al (2002) Brain imaging of the effects of lidocaine on tinnitus. Hear Res 171:43–50.
7. Melcher JR, IS Sigalovsky, JJ Guinan, Jr. et al (2000) Lateralized tinnitus studied with functional magnetic resonance imaging: abnormal inferior colliculus activation. J Neurophysiol 83:1058–72.
8. Schlee W, T Hartmann, B Langguth et al (2009) Abnormal resting-state cortical coupling in chronic tinnitus. BMC Neurosci 10:11.
9. Smits M, S Kovacs, D de Ridder et al (2007) Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway of patients with lateralized tinnitus. Neuroradiology 49:669–79.
10. Lambert RC, T Bessaih and N Leresche (2006) Modulation of neuronal T-type calcium channels. CNS Neurol Disord Drug Targets 5:611–27.
11. Surmeier DJ, J Ding, M Day et al (2007) D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. Trends Neurosci 30:228–35.

12. Wonnacott S, J Barik, J Dickinson et al (2006) Nicotinic receptors modulate transmitter cross talk in the CNS: nicotinic modulation of transmitters. J Mol Neurosci 30:137–40.
13. Slassi A, M Isaac, L Edwards et al (2005) Recent advances in non-competitive mGlu5 receptor antagonists and their potential therapeutic applications. Curr Top Med Chem 5:897–911.
14. Blank T, I Nijholt, MJ Kye et al (2004) Small conductance Ca2+-activated K+channels as targets of CNS drug development. Curr Drug Targets CNS Neurol Disord 3:161–7.
15. Muroi Y and B Chanda (2009) Local anesthetics disrupt energetic coupling between the voltage-sensing segments of a sodium channel. J Gen Physiol 133:1–15.
16. Duckert LG and TS Rees (1983) Treatment of tinnitus with intravenous lidocaine: a double-blind randomized trial. Otolaryngol Head Neck Surg 91:550–5.
17. Israel JM, JS Connelly, ST McTigue et al (1982) Lidocaine in the treatment of tinnitus aurium. A double-blind study. Arch Otolaryngol 108:471–3.
18. Kalcioglu MT, T Bayindir, T Erdem et al (2005) Objective evaluation of the effects of intravenous lidocaine on tinnitus. Hear Res 199:81–8.
19. Lenarz T (1986) Treatment of tinnitus with lidocaine and tocainide. Scand Audiol Suppl 26:49–51.
20. Melding PS, RJ Goodey and PR Thorne (1978) The use of intravenous lignocaine in the diagnosis and treatment of tinnitus. J Laryngol Otol 92:115–21.
21. Merchant SN and N Merchant (1985) Intravenous lignocaine in tinnitus. J Postgrad Med 31:80–2.
22. Trellakis S, J Lautermann and G Lehnerdt (2007) Lidocaine: neurobiological targets and effects on the auditory system. Prog Brain Res 166:303–22.
23. Darlington CL and PF Smith (2007) Drug treatments for tinnitus. Prog Brain Res 166:249–62.
24. Patterson MB and BJ Balough (2006) Review of pharmacological therapy for tinnitus. Int Tinnitus J 12:149–59.
25. Møller AR (2007) Tinnitus: presence and future. Prog Brain Res 166:3–16.
26. Levine RA (2006) Typewriter tinnitus: a carbamazepine-responsive syndrome related to auditory nerve vascular compression. ORL J Otorhinolaryngol Relat Spec 68:43–6; discussion 6–7.
27. Mardini MK (1987) Ear-clicking "tinnitus" responding to carbamazepine. N Engl J Med 317:1542.
28. Tyler R, C Coelho, P Tao et al (2008) Identifying tinnitus subgroups with cluster analysis. Am J Audiol 17:S176–84.
29. Eggermont JJ (2005) Tinnitus: neurobiological substrates. Drug Discov Today 10:1283–90.
30. Enna SJ and M Williams (2009) Challenges in the search for drugs to treat central nervous system disorders. J Pharmacol Exp Ther. 329: 404–11.
31. Spedding M, T Jay, J Costa e Silva et al (2005) A pathophysiological paradigm for the therapy of psychiatric disease. Nat Rev Drug Discov 4:467–76.
32. Henry TR (2003) The history of valproate in clinical neuroscience. Psychopharmacol Bull 37 Suppl 2:5–16.
33. Carpenter WT and JI Koenig (2008) The evolution of drug development in schizophrenia: past issues and future opportunities. Neuropsychopharmacology 33:2061–79.
34. Johannessen Landmark C (2008) Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. CNS Drugs 22:27–47.
35. Bauer CA (2003) Animal models of tinnitus. Otolaryngol Clin North Am 36:267–85.
36. Jastreboff PJ and JF Brennan (1994) Evaluating the loudness of phantom auditory perception (tinnitus) in rats. Audiology 33:202–17.
37. Turner JG (2007) Behavioral measures of tinnitus in laboratory animals. Prog Brain Res 166:147–56.
38. De Ridder D, H Fransen, O Francois et al (2006) Amygdalohippocampal involvement in tinnitus and auditory memory. Acta Otolaryngol Suppl 556:50–3.
39. Jastreboff PJ and MM Jastreboff (2006) Tinnitus retraining therapy: a different view on tinnitus. ORL J Otorhinolaryngol Relat Spec 68:23–9; discussion 9–30.
40. Bauer CA (2004) Mechanisms of tinnitus generation. Curr Opin Otolaryngol Head Neck Surg 12:413–7.
41. Hurko O and JL Ryan (2005) Translational research in central nervous system drug discovery. NeuroRx 2:671–82.
42. Frankenburg FR and RJ Baldessarini (2008) Neurosyphilis, malaria, and the discovery of antipsychotic agents. Harv Rev Psychiatry 16:299–307.
43. Langguth B, R Goodey, A Azevedo et al (2007) Consensus for tinnitus patient assessment and treatment outcome measurement: Tinnitus Research Initiative meeting, Regensburg, July 2006. Prog Brain Res 166:525–36.
44. Vio MM and RH Holme (2005) Hearing loss and tinnitus: 250 million people and a US$10 billion potential market. Drug Discov Today 10:1263–5.
45. Plazas PV, J Savino, S Kracun et al (2007) Inhibition of the alpha9alpha10 nicotinic cholinergic receptor by neramexane, an open channel blocker of N-methyl-D-aspartate receptors. Eur J Pharmacol 566:11–9.
46. Brocco M, A Dekeyne, C Mannoury la Cour et al (2008) Cellular and behavioural profile of the novel, selective neurokinin1 receptor antagonist, vestipitant: a comparison to other agents. Eur Neuropsychopharmacol 18:729–50.
47. Eggermont JJ and H Komiya (2000) Moderate noise trauma in juvenile cats results in profound cortical topographic map changes in adulthood. Hear Res 142:89-101.
48. Norena AJ and JJ Eggermont (2003) Changes in spontaneous neural activity immediately after an acoustic trauma: implications for neural correlates of tinnitus. Hear Res 183: 137–53.
49. Norena AJ, M Tomita and JJ Eggermont (2003) Neural changes in cat auditory cortex after a transient pure-tone trauma. J Neurophysiol 90:2387–401.
50. Muhlnickel W, T Elbert, E Taub et al (1998) Reorganization of auditory cortex in tinnitus. Proc Natl Acad Sci USA 95:10340–3.
51. Norena AJ and JJ Eggermont (2005) Enriched acoustic environment after noise trauma reduces hearing loss and prevents cortical map reorganization. J Neurosci 25:699–705.
52. Norena AJ and JJ Eggermont (2006) Enriched acoustic environment after noise trauma abolishes neural signs of tinnitus. Neuroreport 17:559–63.
53. Stark H and H Scheich (1997) Dopaminergic and serotonergic neurotransmission systems are differentially involved in auditory cortex learning: a long-term microdialysis study of metabolites. J Neurochem 68:691–7.
54. Bao S, VT Chan and MM Merzenich (2001) Cortical remodelling induced by activity of ventral tegmental dopamine neurons. Nature 412:79–83.

55. Kilgard MP and MM Merzenich (1998) Cortical map reorganization enabled by nucleus basalis activity. Science 279:1714–8.
56. Gritti I, L Mainville and BE Jones (1993) Codistribution of GABA- with acetylcholine-synthesizing neurons in the basal forebrain of the rat. J Comp Neurol 329:438–57.
57. Gritti I, L Mainville, M Mancia et al (1997) GABAergic and other noncholinergic basal forebrain neurons, together with cholinergic neurons, project to the mesocortex and isocortex in the rat. J Comp Neurol 383:163–77.
58. Seki S and JJ Eggermont (2003) Changes in spontaneous firing rate and neural synchrony in cat primary auditory cortex after localized tone-induced hearing loss. Hear Res 180:28–38.
59. Lobarinas E, W Dalby-Brown, D Stolzberg et al (2009) Effects of the BK Agonists BMS-204352 and the Enantiomeric Compound ("R-Enantiomer") on Transient, Salicylate Induced Tinnitus in Rats. Association for Research in Otolarygol Baltimore, MD.
60. Nardi A and SP Olesen (2008) BK channel modulators: a comprehensive overview. Curr Med Chem 15:1126–46.
61. Korsgaard MP, BP Hartz, WD Brown et al (2005) Anxiolytic effects of Maxipost (BMS-204352) and retigabine via activation of neuronal Kv7 channels. J Pharmacol Exp Ther 314:282–92.
62. de Lafuente V and R Romo (2005) Neuronal correlates of subjective sensory experience. Nat Neurosci 8:1698–703.
63. de Lafuente V and R Romo (2006) Neural correlate of subjective sensory experience gradually builds up across cortical areas. Proc Natl Acad Sci U S A 103:14266–71.