Deep brain stimulation in tinnitus

Summary

Tinnitus is a common auditory disorder. Most affected persons don't need any medical treatment, however, for some it is a distressing condition. In severely affected patients, it causes severe burden, and is often resistant to conventional treatments. Therefore, there is a need to find effective treatment for severe tinnitus. Lack of knowledge on tinnitus pathophysiology hinders the therapy development. One line of research in therapy development has focused on targeting the affected neurocircuits directly by means of neuromodulation approaches. This requires a better understanding of the disease pathophysiology. In this thesis I studied the pathophysiological mechanisms behind tinnitus in an animal model and human post-mortem tissue. Moreover, I studied the mechanism of action of deep brain stimulation (DBS) as a potential therapy for tinnitus.

Chapter 2 of this thesis reviews the existing evidences on alterations in the medial geniculate body (MGB) in tinnitus. The MGB is the auditory part of the thalamus forming wide connections with limbic regions, which are also suggested to be involved in tinnitus. The MGB was anticipated to be a core region in tinnitus perception in multiple theories. Experimental data shows pathological changes in this region that can contribute to disease pathology. In animal models of tinnitus a higher spontaneous firing rate has been reported in the MGB. Moreover, reduced ambient GABA, increased GABAA receptor, and changes in its oscillations have also been shown. Human neuroimaging studies has shown contradicting outcomes. However, a more consistent finding was a reduced MGB connectivity and possibly its activity in the BOLD fMRI signal. In the review I also discuss a number of clinical studies on thalamus involvement in tinnitus. Thalamic ablation was tested in tinnitus patients and showed a positive effect that reached the total elimination of tinnitus perception. DBS of non-auditory -nearby- regions was accompanied by tinnitus alleviation in movement disorders patients. Additionally, MGB-DBS was able to reduce tinnitus in the noise trauma model of tinnitus. Collectively, the review suggested MGB-DBS as a potential therapy for tinnitus.

In chapter 3 I assessed the changes in activity markers in the auditory and non-auditory areas in a noise trauma model of tinnitus. First, metabolic and neuronal activity markers were investigated in noise-exposed animals and controls using cytochrome c oxidase (COX) and c-Fos, respectively. Noise-exposed animals showed reduced metabolic activity in the primary auditory cortex (AC), MGB, and CA1 of the hippocampus. Neuronal activity marker was increased in the AC in the noise trauma group. Thus, tinnitus affects several regions within the auditory pathway and limbic system. Second, noise-exposed animals were subject to MGB-DBS, which has previously shown to be effective in relieving tinnitus-like behavior. One group received one-hour high-frequency stimulation (HFS) prior to sacrifice and other group served as sham with no stimulation. The stimulated group exhibited higher number of c-Fos positive cells in the thalamic reticular nucleus (TRN) indicating increased neuronal activity. The TRN is a thin layer of GABAergic neurons that send inhibitory feedback to the MGB. This feedback loop is suggested to gate tinnitus signal at the MGB level. Thus, the TRN may act as a mediator in the auditory circuit affected by MGB-DBS to alleviate tinnitus-like behavior.

In Chapter 4, I recorded the evoked potential in the MGB before and after HFS in noise-exposed and non-exposed animals. Sound stimuli were presented with different conditions related to time and temporal regularity. MGB showed the gating capacity signs consistent with the idea

that the MGB serves as a filtering auditory station. Noise exposed group however showed higher evoked potential than non-exposed animals. Also, they failed to show gating signs of temporal regulatory. These could be linked respectively to higher sensitivity and disturbance of gating capacity in the MGB in the noise trauma model of tinnitus. HFS was able to reduce the higher evoked potential but failed to restore the gating of temporal regulatory in the noise-exposed group. The reduction of evoked potential is in line with the finding of increased TRN activity after HFS. Collectively, the results in Chapters 3 and 4 support targeting the MGB with DBS for tinnitus treatment.

Prior to clinical translation of MGB-DBS, findings in animal models of tinnitus need to be validated. In this regard, one important step is to assess the pathophysiological changes in human brain tissue. In chapter 5 I studied the pathological changes in brain samples obtained from tinnitus patients and compared to matched controls. The regions of interest were the MGB, TRN, central part of the inferior colliculus (CIC) and dorsal raphe nucleus (DRN). In tinnitus patients the cell density was reduced only in auditory regions namely the MGB and CIC. No changes were found in the TRN, DRN, or the thalamic visual-related region i.e. the lateral pulvinar when comparing the tinnitus subjects with controls. In the CIC, the cell reduction was accompanied by reduced astrocytes cell count. Then, serotonergic and dopaminergic neurons were quantified in the DRN. Interestingly, a severe reduction in serotonergic cell density was observed without changes in dopaminergic neurons. We then assessed changes of serotonergic cell density in the medullary obscurus raphe nucleus and found a similar change. These findings suggest that tinnitus might be associated with neurodegenerative and inflammatory processes in key auditory regions. Additionally, it implies that serotonergic dysfunction may play role in tinnitus pathophysiology.

I focused on the MGB and CIC in Chapter 6 and investigated the excitatory and inhibitory cell populations. As commonly suggested, tinnitus may arise due to increased activity in related brain regions. Thus, changes in the glutamatergic and GABAergic neuronal population may be an underlying cellular mechanism. The glutamatergic and GABAergic cells were assessed immunohistochemistry. We observe that GAD-immunoreactive (-ir) positive neurons form 10% of the MGB neuronal population. This is considerably higher compared to what has been reported in rodents (less than 1%), which shows the discrepancies between species and could imply that rodents may not be a suitable representative species at least to study the MGB in tinnitus. Moreover, tinnitus samples showed a significant reduction in number of VGLUT2-ir cells in the MGB. No significant change were observed number of GAD-ir positive neurons in the TRN. In the CIC, GAD-ir positive neurons were significantly reduced in tinnitus samples. We did not detect VGLUT-2 signal in the CIC in none of the groups. The reduction of GABAergic neurons in the CIC was expected. However, the reduction of glutamatergic neurons in the MGB contradicts the common hypothesis on mechanism of tinnitus. However, our histological findings are in line with our data in Chapter 5, Chapter 3, and outcomes from human neuroimaging studies. Glutamatergic neurons are more abundant compare to GABAergic neurons in the MGB as shown by us and others in other species. Therefore, they are more likely to be affected in the MGB. Moreover, it implies a reduction in regional activity as shown in Chapter 3 and fMRI studies as well as reduced glutamate in the AC in tinnitus patients.

Finally, all these results were summarized and discussed in Chapter 7, which is followed up with recommendations for future studies.