SUMMARY

The auditory systems of mammals undergo age-related changes resulting in presbyacusis. In the first part of the present thesis, we demonstrate significant changes in the histochemical markers of inhibitory neurons linked to the central component of presbycusis in the inferior colliculus (IC) and the auditory cortex. Our results also demonstrate that the observed changes can be partially attributed to the aging of the central nervous system, while other changes can be dependent on a decline in the ascending activity from the cochlea. For this purpose, we tested two rat strains: the normal aging Long Evans strain with well preserved hearing function up to advanced senescence and the fast aging strain Fischer 344 with a pronounced age-related hearing loss.

In the second part of the thesis, we demonstrate a positive effect of the peroral administration of a drug improving the blood supply to the cochlea (atorvastatin) on the peripheral form of presbycusis. For this purpose we used the C57BL/6J strain of mice, which develops a severe sensorineural hearing loss starting around 3 months of age, and the apoE-/- strain, which usually serves as a standard model of aterogenic hypercholesterolemia.

Changes in the positivity of NADPH-diaphorase(-d) neurons

In the auditory cortex of old Long Evans rats we found a decrease in the number of NADPH-d-positive neurons. Due to the simultaneous reduction in the thickness of the auditory cortex observed in very old rats in this experiment (36 months old), the numerical density of NADPH-d-positive neurons was significantly increased compared to young animals. In additon, the number of dendritic segments and branching points of the neurons in old animals were increased, whereas the average length of a dendritic segment was decreased. Consequently, the mean value of the total length of visible dendritic segments per neuron remained similar between young and old rats. The decrease in the number and the remodelling of NADPH-d-positive neurons may contribute to, or be associated with, functional age-related changes in the central auditory system.

Changes in the immunoreactivity of parvalbumin (PV)

In the IC of old Long Evans rats we found an increase in the number and optical density of PV-ir neurons, whereas in the auditory cortex of this strain the changes were not significant. In old Fischer 344 rats, a tendency towards decreased numbers of PV-ir neurons in the IC was accompanied by a significant reduction in the volume of PV-ir somas. Moreover, in the auditory cortex of this strain we observed large deficits in the local occurrence of PV-ir neurons, resulting in a significant reduction of their mean numerical density. Nevertheless, in sections stained for Nissl substance, no significant changes in the total number of neurons were present. The large reduction in the number of PV-ir neurons in the auditory cortex of Fischer 344 rats could be a consequence of a decline in afferent activity due to peripheral hearing loss. However, the contribution of general pathological changes in the brain with aging should be considered because similar reductions were also found in the visual and retrosplenial cortices in this strain. On the other hand, the well-preserved hearing function in old Long Evans rats could be associated with the preserved function of the parvalbumin neurons in the auditory pathway.

Changes in the immunoreactivity of glutamate decarboxylase (GAD)

Despite the fact that PV-ir cells form a significant subpopulation of GABA-expressing neurons, the age-realated changes in the levels of GAD (GAD65 and 67 isoforms), the key enzyme for the synthesis of GABA, were rather different. Our findings in the inferior colliculus and auditory cortex demonstrated a uniform character of age-related changes in both strains comprising a decrease in the number of GAD65- and 67-ir cells, a decrease in the optical density of immunoreactive somas and reduced levels of GAD65 and 67 proteins (by 50%) compared to young animals as detected by western blotting. A less pronounced decline in the immunoreactivity of GAD was also found in the visual cortex of both strains. Therefore, we suggest that the age-related decline in GAD expression in the IC and auditory cortex does not depend on peripheral deafferentation but represents a feature of the aging brain.

The influence of atorvastatin on age-related hearing deterioration in C57BL/6J and apoE$^{-/-}$ mice.

Changes in the distortion products of otoacoustic emissions (DPOAE) represent a sensitive and early indicator of outer hair cell loss. In C57/BL/6J mice, significantly larger DPOAE amplitudes were found after 8-week atorvastatin treatment. For higher frequencies (19-27 kHz), the difference was unambiguously significant. A significant decrease in the levels of inflammatory endothelium markers in the aortic wall confirmed the positive effect of atorvastatin in these animals. The corresponding finding of no changes in blood cholesterol levels demonstrates that the effect of atorvastatin is not mediated through lowering the levels of lipids in the blood. No such beneficial effect of statins was found in apoE-/- mice treated with atorvastatin under the same conditions. In conclusion, the results of our experiments demonstrate that atorvastatin may slow down the deterioration of hearing function with age, at least in the animal model of sensorineural presbycusis.