hormones and other extracellular activators to intracellular pathways. PIP3 signaling, in particular, is associated with the control of cell survival and cell death. PIP3 binds to and activates the phosphoinositide-dependent protein kinase-1 which, in turn, phosphorylates and activates the downstream target Akt which leads to phosphorylation of numerous downstream proteins targets. Akt is a major hub for intersecting pathways affecting cell growth, cell survival, and cell differentiation. It appears to be pivotal as an anti-apoptotic factor in many different cell death paradigms. We investigated this crucial survival pathway in three models of acquired hearing loss using CBA/J mice: kanamycin-induced deafness, noise trauma, and age-related sensorineural hearing loss. Immunostaining on cochlear cryosections revealed a rather wide-spread distribution of PIP3 in the cochlea which was markedly attenuated following any of the three insults. Consistent with a reduction of PIP3, the phosphorylation of the downstream target Akt at threonine 308 also significantly decreased in outer hair cells. Since the levels of PIP3 are reciprocally controlled by phosphoinositide 3-kinase and the phosphatase PTEN (phosphatase and tensin homologue deleted on chromosome ten) we began investigating the expression of theses enzymes. Preliminary results show increased PTEN activity in aging cochleae suggesting a decline of the survival capacity of traumatically affected outer hair cells via PIP3/Akt signaling due to an increase of PTEN.

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688 Transient-Receptor-Potential Channel TRPM3 Deficiency Leads to Noise Vulnerability and Progressive Hearing Loss in Mice

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Transient-receptor-potential channels (TRPs) are a heterogeneous family of transmembrane proteins that vary by their activation mechanisms and cation selectivities. Some of the TRPs have been proposed to be involved in cochlear function or to be candidates for proteins involved in the hair cell transduction process. However, the role of many other TRP variants for hearing is still unclear.

TRPM3 has not been described in the inner ear so far and the expression and function in the cochlea and auditory brain structures are unknown. Using TRPM3 specific primerpairs and riboprobes we could detect TRPM3-transcripts in the inner ear of rat and mouse. Within the inner ear, TRPM3 was abundant in the stria vascularis and spiral ganglion. RT-PCR-analysis showed TRPM3 transcripts also in the apical and basal turns of the organ of corti and in isolated inner and outer hair cells.

To examine the role of TRPM3 in auditory function we generated a TRPM3-deficient mouse line by deletion of the pore coding region of the TRPM3 gene and analyzed auditory evoked brainstem responses (ABR) and distortion product otoacoustic emissions (DPOAE). Hearing of young TRPM3-deficient mice was similar as compared to wildtype littermate controls although TRPM3-deficient mice were already significantly more vulnerable to acoustic overstimulation. In aged TRPM3-deficient mice, spontaneous hearing functions were significantly affected.

The pattern of hearing loss will be analyzed in respect to inner and outer hair cell function and correlated with the expression pattern and phenotype of the inner ear in TRPM3-deficient mice. We propose an important role of TRPM3 channels in the inner ear for retention of normal function and for the response to excitatory overstimulation.

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689 Susceptibility to Noise-Induced Hearing Loss in Two Congenic Mouse Strains

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In 1993 Erway et al. identified a single genetic locus (*Ahl*) that could explain the early presbycusis observed in the inbred C57BL/6J mouse strain. This locus was later shown to make this strain more vulnerable to noise-induced hearing loss (Davis et al., 2001). This locus is believed to code for cadherin 23.

Recently, Johnson has developed two relevant congenic mouse strains. In the congenic C57BL/6J strain, the *Ahl* locus has been replaced by the wild-type locus from the inbred CBA/CaJ strain (strain B6.CBA). In the congenic CBA/CaJ strain the wild-type locus has been replaced by the mutant *Ahl* locus (strain CBA.B6). The present study was designed to test these congenic strains for their vulnerability to noise-induced hearing loss.

Mouse hearing was tested pre-exposure by ABR at 8, 16 and 32 kHz. Groups of both strains were exposed to various levels of broadband noise between 98 and 118 dB for one hour. Seven to nine days later their hearing was again tested by ABR.

Generally, pre-exposure the B6.CBA congenics started out with more sensitive ABR thresholds than the CBA.B6s (strain differences were statistically significant at all frequencies pre-exposure.) This would be expected based on the fact that the congenic CBA.B6 mice genotypes included the mutant *Ahl* locus.

This presentation will compare ABR results in the two congenic strains as well as compare the present data with the previous inbred C57BL/6J and CBA/CaJ data.

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