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The built cochlea: a guided tour

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Human hereditary deafness: from genes to cochlear pathogenesis

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A KCNQ-type potassium current in cochlear inner hair cells

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Cochlear inner hair cells (IHCs) transduce sound-induced vibrations into a receptor potential that controls afferent synaptic activity and, consequently, frequency and timing of action potentials in the postsynaptic auditory neurons. The receptor potential is thought to be shaped by the two voltage-dependent K^+ conductances, $I_{K,f}$ and $I_{K,s}$, which are carried by BK-type and K_V-type K^+ channels.

Using whole-cell voltage-clamp recordings in the acutely isolated mouse cochlea we show that an additional K^+ current is present in IHCs. This current is active at the resting membrane potential (−72 mV) and deactivates upon hyperpolarization. It is potently blocked by the KCNQ channel blockers linopirdine and XE991, while it is insensitive to tetraethylammonium (TEA) and 4-aminopyridine (4-AP), which inhibit $I_{K,f}$ and $I_{K,s}$, respectively. Immunocytochemistry showed expression of the KCNQ4 subunit in IHCs, indicating that the novel K^+ current is mediated by KCNQ4 channels. In current-clamp experiments, block of the KCNQ4-current shifted the resting membrane potential by about 7 mV to −65 mV and led to a significant activation of BK channels. Using BK channels as an indicator for intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), it is shown that the shift in IHC resting potential observed upon block of KCNQ4 leads to an increase in $[Ca^{2+}]_i$ to micromolar concentrations. In conclusion, our results show that KCNQ4 channels set the resting membrane potential in cochlear IHCs, and thereby contribute to the maintenance of low$[Ca^{2+}]_i$. Destabilization of the resting potential and an increase in $[Ca^{2+}]_i$ as may result from impaired KCNQ4 function in IHCs provides a novel and straightforward explanation for the progressive hearing loss (DFNA2) observed in patients with defective KCNQ4 genes.

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Postsynaptic currents at the inner hair cell ribbon synapse

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Hair cells, like retinal photoreceptors release their transmitter continuously, modulating the rate of release as stimulus intensity changes. Both cell types have a presynaptic specialization, the synaptic ribbon, that is thought to accumulate or promote the release of vesicles. What are the mechanisms that allow continuous and rapid release at the hair cell synapse? Capacitance measurements have shown that hair cells can sustain high rates of membrane fusion, possibly corresponding to the release of hundreds of vesicles per ribbon per second (Moser & Beutner, 2000). We investigated the inner hair cell synapse in the postnatal rat cochlea by recording excitatory postsynaptic currents from afferent terminals contacting the inner hair cell. We propose from our data that the ribbon synapse operates by multivesicular release. I shall compare the quantitative analysis of capacitance measurements of vesicular fusion in hair cells and the analysis of postsynaptic currents at the IHC afferent synapse. We find both methods lead to similar results. I shall also discuss the comparison of anatomical data of the postnatal and the adult ribbon synapse. How much can we learn about the transmitter release mechanism in the adult cochlea from recordings in the immature system?

Moser T & Beutner D (2000). *Proc Natl Acad Sci* **97**, 883.

SA36

How the ear influences auditory brainstem development: signals, cellular events and critical periods

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Since the classic experiments of Hubel and Wiesel, a large variety of studies have shown that manipulations of sensory experience can have profound influences on the development of sensory encoding pathways of the central nervous system. Yet little is known about the cellular mechanisms whereby changes in sensory system function influence the structure or integrity of CNS elements. We have used the brainstem auditory pathways of birds and mammals to investigate the early cellular events underlying deprivation- and deafferentation-induced changes in the structure and integrity of neurons and glial cells. I will discuss a series of *in vivo* and *in vitro* experiments which address three issues related to activity-regulated development and maintenance of cochlear nucleus neurons. What is the nature of the intercellular signals regulating structural integrity of postsynaptic neurons? What are some of the intracellular cascades of events underlying deprivation-induced changes in neuronal integrity? What biological mechanisms may underlie developmental differences in responses to peripheral manipulations (critical periods)?

To address the first question, a series of experiments were designed to independently manipulate patterned acoustic information, spontaneous eighth nerve activity, presynaptic stimulation and postsynaptic action potential generation. We were able to conclude that the necessary and sufficient condition

for maintaining a normal compliment of cochlear nucleus neurons is stimulation of membrane-bound glutamate receptors. Studies of the dynamic cellular events subsequent to deprivation reveal disinhibition of a unique signalling pathway involving metabotrobic glutamate receptor regulation of intracellular calcium. A working model suggests that when ongoing activation of this pathway is interrupted, elevated intracellular calcium activates an apoptotic-like cascade resulting in rapid cell death or cell atrophy in the target neurons. Finally, recent experiments using normal and transgenic mice are consistent with the hypothesis that the differential susceptibility of neonatal and adult sensory systems to deprivation of afferent activity (critical periods) may be due to changes in the expression of apoptotic response genes of the caspase and bcl-2 families.

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Adjustment of ITD sensitivity in the medial superior olive depends on early experience

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Interaural timed differences (ITD) are the dominant cue for localizing low frequency sounds in the azimuthal plane. In mammals, ITDs are initially encoded by neurons of the medial superior olive (MSO). Our recent *in vivo* recordings from gerbil MSO neurons with pharmacological blockade of glycinergic inhibition (Brand *et al.* 2002) show that binaural excitation leads to ITD sensitivity with maximal discharges around zero ITD. Consequently, the maximal slopes of the resulting ITD functions are mostly outside the physiological relevant range of ITDs. Exquisitely well-timed glycinergic inhibition, however, adjusts these ITD functions to peak at 0.12 cycles of each neuron's best frequency, thereby bringing the steep slope into the relevant range. It has been shown earlier that this glycinergic input to the MSO undergoes an experience-dependent redistribution in the first days after hearing onset (Kapfer *et al.* 2002). We hypothesized that this structural change should be related to the function of inhibition, hence, the precise and proper timing. In animals with abnormal distributions of inhibitory inputs ITD sensitivity should not be adjusted as in control animals. To test this, we recorded from ITD-sensitive auditory brainstem neurons in gerbils with normal development and compared it with that in animals that were reared in omnidirectional noise and animals that were exposed to the same noise as adults. The latter group of animals showed ITD tuning similar to that found in the control group. However, in noise-reared animals, the ITD sensitivity was not adjusted to bring the maximal slope into the physiologically relevant range and resembled that found in the MSO during blockade of glycinergic inhibition.

Our findings show that well-timed inhibition is essential for the fine-tuning of ITD functions. Moreover, auditory experience is essential for developing the proper timing of inhibitory inputs, apparently by selective removal of inhibitory inputs on MSO cells.

Brand A *et al.* (2002). *Nature* **417**, 543.

Kapfer C *et al.* (2002). *Nature Neurosci* **7**, 247.

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SA38

Hearing-aid signal processing for sensorineural (cochlear) losses

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Cochlear hearing loss often involves loss of function of the outer and inner hair cells within the cochlea, although there may also be metabolic disturbances and structural abnormalities. Loss of outer hair cell function has the following perceptual effects:

(1) loss of absolute sensitivity (related to reduced amplitude of vibration on the basilar membrane);

(2) loss of frequency selectivity, associated with broader tuning on the basilar membrane, which contributes to difficulties in understanding speech, especially in noise;

(3) an abnormally rapid growth of loudness with increasing intensity (recruitment) associated with steeper input-output functions on the basilar membrane.

The first and third of these effects can be compensated by amplification combined with automatic gain control (AGC), although there is still much controversy about the 'best' way of implementing AGC. The second effect cannot be fully compensated, although directional microphones can be helpful, and digital processing to increase spectral contrast may be of some benefit.

Loss of inner hair cell function has the following perceptual effects:

(1) loss of absolute sensitivity (related to less efficient transduction);

(2) more noisy transmission of information to the central auditory system, which contributes to difficulties in understanding speech;

(3) in extreme cases ('dead regions'), no transduction from certain regions of the cochlea.

Effect (1) can be compensated by amplification, but effects (2) and (3) are much more difficult to deal with. Again, directional microphones can help. There is some evidence that 'transposition' (transforming high frequencies to lower ones) can be beneficial for people with dead regions. The combination of a hearing aid and a cochlear implant may also be beneficial.