Functional Recovery of Hearing after Inner Ear Trauma

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Introduction

The inner ear receptor cells, hair cells, are susceptible to a variety of traumata. Hair cell damage can result from sound-overexposure, ototoxic drugs, infective, autoimmune and genetic diseases and comes along with aging. Hair cell loss in the mature mammalian inner ear, including that of man, causes permanent hearing loss, because lost hair cells are not replaced. Damage and loss of hair cells is followed by degeneration of the hair cell synapses and the afferent nerve fibres of the auditory nerve. Mechanisms that may contribute to restoration of hearing are reviewed briefly below.

Conservation of hearing

The first imperative to preserve hearing is to prevent damage to the hair cells and nerve fibres. Avoiding long loud sound exposure, one of the most common causes of hearing loss, is obviously a most important protector of hearing. Beyond that, several agents have been shown to have a potential to protect hair cells and nerve fibres against trauma. Among these are anti-oxidant drugs, that reduce the level of cellular reactive oxygen species [1]. Anti-apoptotic drugs can stop the trauma induced apoptotic death of hair cells [2]. Glutamate-antagonists can reduce excitotoxic damage of the hair cell transmitter to the afferent nerve terminals [3]. Growth factors can protect the ear and especially the nerve fibres against trauma [4].

An example of a protective effect of the neurotrophic factor NT-3 on hearing loss induced by the ototxic antibiotic kanamycin is shown in Figure 1 [5]. Intracochlear application of NT-3 results in reduced threshold loss after kanamycin induced trauma.

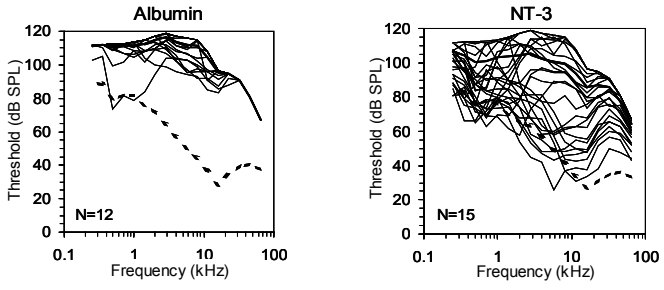

Figure 1: Thresholds auditory evoked potentials from the inner ears of guinea pigs deafened by systemic application of kanamycin. Dashed line represents normal threshold. Left panel: control animals given kanamycin alone. Right panel: effect of intracochlear application of NT-3 on kanamycin induced hearing loss.

Regeneration of lost hair cells

Once hair cells are lost, they must be replaced before any functional recovery is possible. Spontaneous regeneration of hair cells, which does not occur in the mammalian inner ear, is common in non-mammalian vertebrates. Hair cell regeneration has been most extensively studied in birds [6]. Lost hair cells in the avian inner ear are spontaneously replaced by proliferation of supporting cells that differentiate to hair cells, as well as transdifferentiation of supporting cells to hair cells [7]. The regenerated hair cells reconnect to the accessorial structures and become innervated. This process is accompanied by substantial recovery of function [8].

Using locally applied gentamicin at the round window of the inner ear, we succeeded in destroying all hair cells in the basal 50% of the pigeon receptor epithelium. This area processes auditory frequencies of 400-6000 Hz. After an initial hearing loss of 60-70 dB in this frequency range, spontaneous functional recovery occurred, beginning at two weeks after deafening, proceeding up to 4 weeks. Despite substantial functional recovery a threshold loss of up to 30 dB remains (Figure 2).

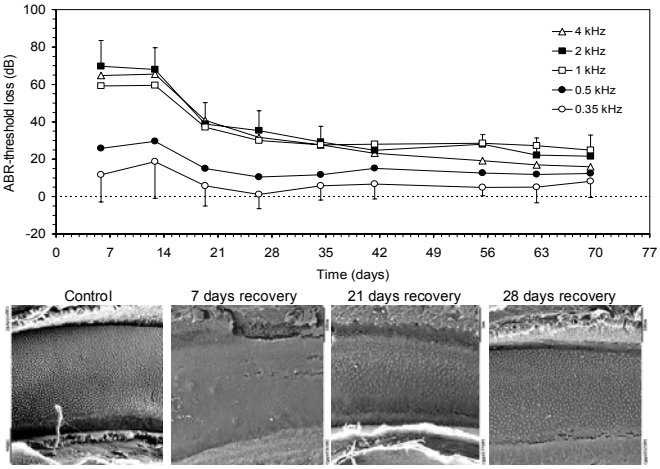

Figure 2: Top: Thresholds of auditory brain stem evoked potentials at different frequencies in the pigeon after destruction by gentamicin and subsequent spontaneous regeneration of hair cells in the frequency range 400-6000 Hz. Bottom: scanning electronmicgraphs (460 x 460 µm) of a control ear and after 7-28 days of recovery. Complete loss of hair cells at day 7, nearly complete regeneration at day 28.

In mammalian inner ears the supporting cells, that give rise to new hair cells in the avian inner ear, are in a terminally differentiated state and not capable of proliferation or transdifferentiation. However, this might be induced by eliminating inhibitory factors or supply of stimulating factors. Proliferation of supporting cells is extended into the early postnatal period in knock-out animals for p27Kip1, an inhibitor of cell cycling [9]. Even proliferation of hair cells is possible in vivo by inactivation of pRb (Retinoblastomprotein) that normally inhibits transcription factors that induce cell proliferation [10]. Another possibility might be to replace the lost hair cells by transplantation of cells into the inner ear [11], or to induce transdifferentiation

of supporting cells, as shown by upregulation of Math1 [12] or Hath1 [13]. However, replacement of the hair cells is far from being sufficient to restore hearing. In addition to control the replacement of the hair cells, it is necessary that they are integrated in the epithelium, reconnect to the inner ear mechanics and become functional and innervated, in order that functional recovery of hearing may occur. We are at the moment far from achieving this challenging task. Nevertheless, since replacement of hair cells in the mammalian cochlea appears feasible, it might be possible to achieve functional recovery on this basis, once the underlying mechanisms are understood and become controllable [14].

Repair mechanisms

Despite absence of hair cell regeneration in mammals, a moderate degree of functional recovery can regularly be observed after cochlear damage. This recovery is based on repair mechanisms of surviving structures. For instance the initial ABR threshold shifts after exposure to loud sound recover to a certain extent early after damage (Figure 3).

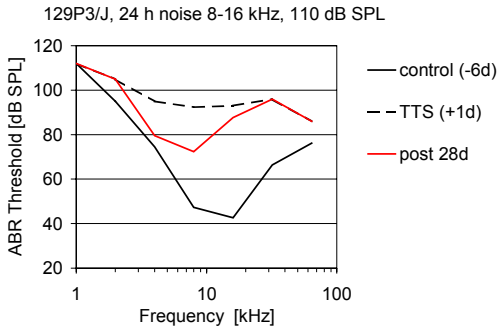

Figure 3: ABR threshold in the mouse before (control) and one (TTS, temporary threshold shift) and 28 days after after after loud noise exposure.

The observed rapid turnover of actin in the hair cell stereocilia may allow for significant repair [15].

A significant part of the initial acute threshold loss after sound overexposure relies on the excitotoxic effect of massive transmitter release during loud stimulation, which destroys the synapses of the auditory nerve fibres [16]. We investigated this process in the pigeon, using the glutamate agonist AMPA [17]. Instillation of AMPA into the scala tympani of the inner ear leads to immediate abolition of compound action potential (CAP) responses. Following AMPA treatment the nerve terminals showed swelling and degeneration, followed by recovery over a period of about a week. CAP thresholds recovered over a period of three weeks, however with a permanent deficit at high frequencies (Figure 4).

Compensation and prostheses

Finally functional restitution of hearing after peripheral damage can be achieved by compensatory plastic changes in the auditory pathway [18] or ultima ratio by hearing aids or cochlear implants [19].

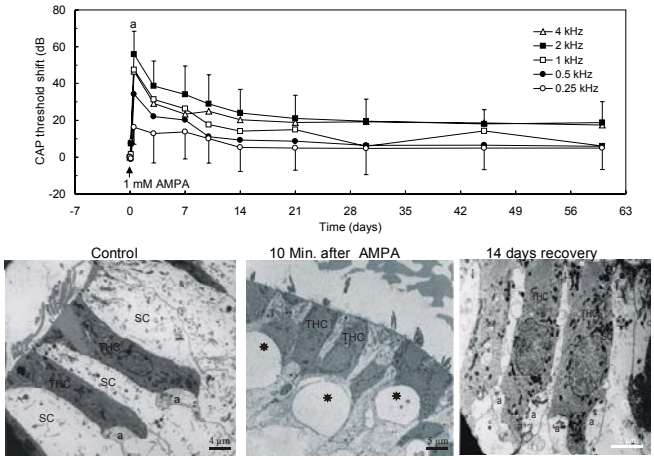

Figure 4: Top: Time course of compund action potential thresholds from the inner ear of pigeon after acute trauma by the glutamate agonist AMPA. Bottom: Micrographs of hair cell – neural synapyses before (control), immediately after (10 min.) and 14 days after trauma. THC: hair cells, SC: supporting cells, *: swollen terminals

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