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# The Mongolian Gerbil as a Model for the Analysis of Peripheral and Central Age-Dependent Hearing Loss

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## 1. Introduction

Age-dependent hearing loss involves pathological changes affecting the peripheral as well as the central auditory system. The Mongolian Gerbil is a rodent with an average life span of 3-4 years, which shows, in contrast to mice and rats, sensitive hearing in the frequency range that is important for human communication. Consequently, gerbils have been used to study structural and functional aspects of age-dependent hearing loss at the level of the cochlea and auditory brain stem nuclei. In addition, age-dependent changes in behavioural performance have been characterised for different auditory tasks. We have also analysed the effect of certain drugs on impaired temporal processing in old gerbils. The data from gerbils contribute to a framework that helps to better understand the mechanisms contributing to age-dependent hearing loss and may lead to new pharmacotherapeutic strategies for the treatment of age-dependent central hearing loss.

## 2. Gerbils as model organism

Like mice and rats, gerbils are small rodents. Henceforth, when we use the term gerbil, we refer to the species *Meriones unguiculatus*. The natural range of distribution of this species is Mongolia and the adjacent regions of Siberia and China. The first description of the species was by Milne Edwards in 1867 (Milne-Edwards, 1867). The history of the "laboratory gerbil" has been summarised by Stuermer et al. (2003). Briefly, a small group of 20 wild pairs were originally collected in 1935 during a Japanese expedition to Mongolia and subsequently bred in Japan. In 1954, eleven pairs from this Japanese colony were sent to Tumblebrook Farm in New York. Offspring of the Tumblebrook Farm breeding colony have subsequently been distributed worldwide and are used as models for different lines of research. A search for the term "gerbil" in combination with the terms "hearing", "ear" and "auditory" on Sept. 7<sup>th</sup> 2011 in the PubMed database lists 1405 publications, illustrating that gerbils have become an important model in auditory research.

The sensitivity of gerbils at low frequencies important for speech perception is similar to that of humans, while thresholds of rats and mice are much higher for frequencies below 4 kHz (Fig. 1). Thus, gerbils appear to be a better model than mice and rats to study aspects of age-dependent hearing loss that affect communication and speech perception in older

human subjects. Gerbils have been suggested as a particularly suitable model for research on diverse aspects of ageing, including audition (Cheal, 1986). Here we will review the studies of age-dependent changes in the auditory system of gerbils.

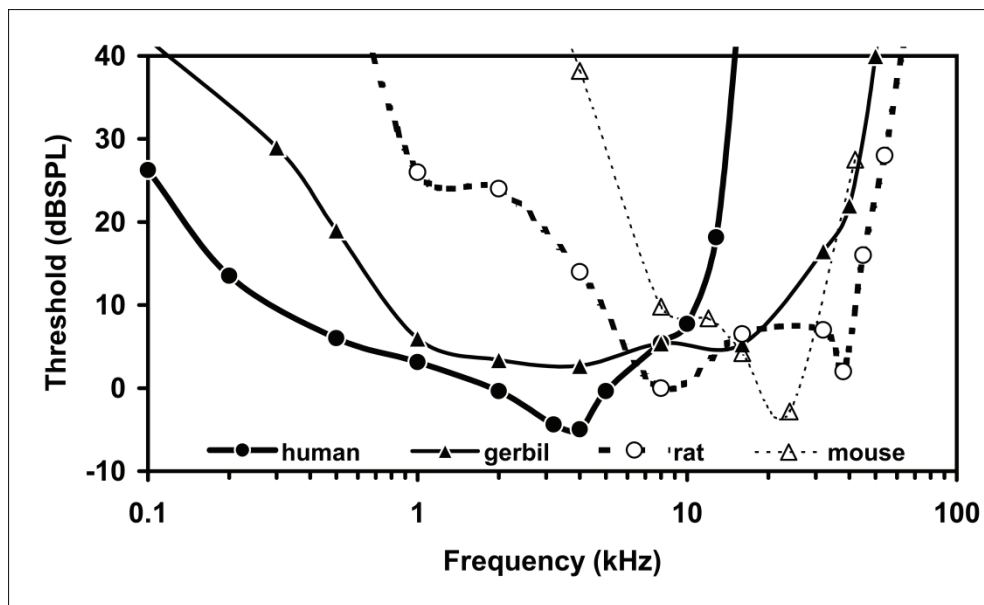


Fig. 1. Audiograms from human, gerbil, rat and mouse

The human audiogram (filled circles, thick continuous line; Zwicker & Fastl, 1990) shows the lowest thresholds at low frequencies. The gerbil audiogram (filled triangle, black continuous line; Ryan, 1976) is similar to the human audiogram, but the hearing range of gerbils extends to frequencies above 20 kHz. Compared to human and gerbil, thresholds of rat (open circles, thick dotted line; Kelly & Masterton, 1977) and mouse (open triangles, thin dotted line; Radziwon et al., 2009) are much higher for frequencies below 4 kHz.

### 3. The cochlea

Comparative studies (Webster & Plassmann, 1992) show that the low-frequency hearing in gerbils is associated with adaptations of the middle ear (e.g. large middle ear cavities that facilitate the transmission of low frequencies to the inner ear) and of the basilar membrane (e.g. increased width compared to other small rodents).

#### 3.1 Activity of single auditory nerve fibres

Analysis of auditory nerve fibre activity provides information about sound processing in the cochlea. A reference species, in which auditory nerve fibre function has been studied in much detail, is the cat (Kiang, 1965). In a comparative analysis of gerbil auditory nerve fibre activity, Schmiedt (1989) demonstrated a good correspondence with data from the cat and suggested that this "implies the presence of fundamental mechanisms that are common to

mammalian auditory systems”, making the gerbil a useful model for hearing loss in ageing studies.

In addition to normative data gathered using young gerbils, several studies have also analysed auditory nerve fibre activity in gerbils older than 1 year. In auditory nerve fibres of quiet aged three-year-old gerbils, Schmiedt et al. (1990) found that thresholds were elevated by 20-30 dB at the tip (characteristic frequency, CF) of the tuning curves, while the low frequency tails were much less affected, resulting in a reduced tip-to-tail ratio. Measures of frequency selectivity, like  $Q_{10\text{dB}}$  and  $Q_{40\text{dB}}$  (Hellstrom & Schmiedt, 1996), were similar for young and old gerbils in fibres with CFs below 4 kHz, while auditory nerve fibres with higher CFs were on average less sharply tuned in old gerbils. A comparison of rate-level functions (the discharge rate of auditory nerve fibres plotted as a function of stimulus level) at CF in old and young gerbils showed that these functions in old gerbils were shifted to higher levels, consistent with elevated thresholds of auditory nerve fibres. However, the slopes of functions in the dynamic range region between threshold and saturation of old gerbils were at least as steep as those from young gerbils. The distributions of spontaneous rates in large samples of auditory nerve fibres from young and old gerbils were similar for fibres with CFs below 6 kHz, while the proportion of low spontaneous rate fibres with CFs above 6 kHz was only 30% in old gerbils, compared to 60% in young gerbils (Schmiedt et al., 1996). Fibres with low spontaneous activity typically have higher thresholds and larger dynamic ranges compared to fibres with high spontaneous rates (Winter et al., 1990). Thus, a loss of the contribution of auditory nerve fibres with low spontaneous rate may affect processing of supra-threshold signals and contribute to a decreased ability to understand speech in noise.

### **3.2 The compound action potential (CAP)**

Although single-fibre recordings provide much information, the amount of data that can be generated in an individual gerbil, especially in aged animals, is limited. An alternative to evaluate the state of the cochlea is the compound action potential (CAP), an electrical signal that is generated by the synchronised population response of the auditory nerve fibres to the onset of a signal (Hellstrom & Schmiedt, 1996).

#### **3.2.1 CAP threshold and growth with stimulus intensity**

By plotting CAP thresholds across a range of test frequencies, Hellstrom & Schmiedt (1990) compared CAP audibility curves of young and old gerbils and found a varying degree of frequency-specific threshold elevation in old gerbils. Compared to young gerbils, the inter-animal variability of thresholds was much higher in old gerbils for frequencies above 3 kHz. Below 3 kHz, old gerbils showed an average of less than 20 dB threshold elevation, while the difference increased at higher frequencies to more than 30 dB. The growth of the peak-to-peak CAP amplitude with increasing level of the tone pip was considerably reduced in old gerbils and a quantitative analysis confirmed that the slopes of the CAP input-output functions were significantly reduced for test frequencies between 1 and 8 kHz. While the elevated CAP thresholds in old gerbils reflect the elevated thresholds at the tip of the tuning curve in recordings from auditory nerve fibres (Schmiedt et al., 1990), the reduced slope of the CAP growth functions in old gerbils was not reflected in the rate-level functions of auditory nerve fibres (Hellstrom & Schmiedt, 1991). Given that the slopes of rate-level

functions of auditory nerve fibres did not differ between young and old gerbils, Hellstrom & Schmiedt (1990, 1991) argued that a loss of auditory nerve fibres and spiral ganglion cells and a loss of synchrony of the auditory nerve fibre population response could result in reduced CAP amplitudes in old gerbils.

### **3.2.2 CAP measure of cochlear frequency selectivity**

CAP measurements have also been conducted to compare cochlear frequency selectivity of young and old gerbils (Hellstrom & Schmiedt, 1996). A forward masking paradigm was used to determine masked CAP tuning curves at probe frequencies between 1 and 16 kHz. Briefly, a probe of a given frequency was presented 10-15 dB above the CAP threshold, eliciting a robust CAP response. The response to the probe was masked by a 60 ms tone burst that was presented 5 ms before the probe. The masked CAP tuning curve was obtained by plotting the masker level that just suppressed the response to the probe as a function of masker frequency. The masked CAP tuning curves share many characteristics with auditory nerve fibre tuning curves. The elevation of threshold at the tip of single fibre tuning curves in old gerbils (Schmiedt et al., 1990), especially at higher frequencies, was also evident in masked CAP tuning curves. In addition, the loss of frequency selectivity in auditory nerve fibres with characteristic frequencies above 4 kHz in old gerbils was paralleled by a corresponding loss of frequency selectivity in the masked CAP tuning curves (Hellstrom & Schmiedt, 1996).

### **3.3 Distortion product otoacoustic emissions (DPOAE)**

Distortion product otoacoustic emissions (DPOAE) characterise the function of outer hair cells that are the central element of the "cochlear amplifier". They can be used to determine the sensitivity of the cochlea and to construct audiograms (Janssen et al., 2006). Eckrich et al. (2008) measured DPOAE audiograms of "laboratory" gerbils and gerbils that had been caught in the wild and bred for 6-7 generations in captivity. While thresholds of "wild" gerbils remained stable across age, thresholds of 15-28 month old, domesticated gerbils were increased at 2 kHz (6 dB), between 8 and 20 kHz (6-11 dB) and above 44 kHz (6-12 dB), when compared to the thresholds of 3 and 6 month old, domesticated gerbils. For the most basal test frequencies above 50 kHz, threshold elevation of more than 6 dB was present in the 9 and 12 month old, domesticated gerbils. Eckrich et al. (2008) suggested that elevated DPOAE thresholds in the older gerbils may have been caused by a loss of the endocochlear potential and/or a loss of outer hair cells.

### **3.4 Age-dependent hair cell loss**

The loss of hair cells is one mechanism that causes hearing loss. Cytocochleograms are plots of the proportion of missing and abnormal hair cells as a function of the position along the cochlea. When the cochlear place-frequency map is known, frequency specific hearing loss can be directly correlated with hair cell loss. Tarnowski et al. (1991) performed such a comparison of cytocochleograms and CAP thresholds in 16 old gerbils raised in a low-noise environment. In their sample, they found a substantial inter-animal variation of threshold shift and hair cell loss and defined 3 groups based on the degree of hair cell loss. In 6 animals with minimal hair cell loss (5-8%), only outer hair cells were missing,

predominantly in the apical turn and to a lesser degree in the extreme basal turn. This group of animals showed the least degree of threshold elevation (0-25 dB). Eight animals with a moderate degree of hair cell loss (8-14%) showed, on average, higher degrees of threshold shift (5-55dB). Outer hair cell loss was more pronounced at the apex, but was also present towards the base of the cochlea. In 2 gerbils, 41-54% of the hair cells, predominantly outer and to a lesser degree inner hair cells, were missing. The hair cell loss in this group was associated with more than 50 dB hearing loss. In addition to hair cell loss, a varying proportion of outer hair cells in the low-frequency (apical) region of old gerbils appeared grossly abnormal with a spherical shape and larger diameters. These cells were located between normally appearing outer hair cells. No such abnormalities were found in young animals. Although the degree of hair cell loss was associated with the degree of threshold shift in the 3 groups, the pattern of hair cell loss did not correlate with the frequency-dependent CAP threshold shifts along the cochlea. Loss of outer hair cells at the apex was found without corresponding threshold shifts for frequencies below 3 kHz. Above 4 kHz, threshold shift was present without a loss of outer hair cells in the corresponding frequency region. These data demonstrate that cytochleograms cannot predict the frequency-specific CAP threshold shifts in old gerbils raised in a low noise environment.

### **3.5 Pathology of non-sensory cells in the organ of Corti and Reissner's membrane**

Adams & Schulte (1997) expanded the analysis of cochlear pathology in old gerbils to the non-sensory cells of the organ of Corti and Reissner's membrane. In addition to the loss and pathology of hair cells, they observed pathological changes to pillar cells in regions where outer hair cells had been lost. Compared to young gerbils, where the cells forming Reissner's membrane appeared uniformly distributed, gerbils older than 2 years showed a formation of cell clusters mixed with regions of lower cell density. However, this rearrangement of cells in Reissner's membrane appeared to not be related to hearing loss. In summary, Adams & Schulte (1997) emphasised the discrepancy between the frequencies affected by hearing loss and the position of cell pathology along the cochlea.

### **3.6 Spiral ganglion cells and auditory dendrites**

Keithley et al. (1989) compared the density of spiral ganglion cells in young and old gerbils. The mean ganglion cell density averaged along the whole cochlea was 1106 cells/mm<sup>2</sup> for 4 gerbils with an age of 2 months. Compared to the mean of these young gerbils, the density decreased to 86% and 83% in 5 animals aged 24-30 months and in 3 animals aged 36-42 months respectively, though the difference between the young animals and the 2 groups of old animals was not significant in this sample. When they compared mean spiral ganglion cell density for separate half turns of the cochlea, a significant reduction that varied between 16 and 55% in the two groups of old gerbils with reference to the 2 month old animals was only found for the most basal position (80-90% from the apical end, corresponding to frequencies above 20 kHz). Overall, the loss of spiral ganglion cells was limited and predominantly affected high frequencies.

Based on a small sample that precluded statistical analysis, Suryadevara et al. (2001) suggested a slightly decreased number of auditory dendrites per inner hair cell in old gerbils. Their data in young gerbils showed a gradient of auditory nerve fibre dendrite

diameter within the osseous spiral lamina, with increasing diameter from the scala vestibuli to the scala tympani side. With decreasing endocochlear potential (EP) in old gerbils, this gradient disappeared due to fewer large diameter fibres found near scala tympani. In addition, the cross-sectional area of spiral ganglion cells decreased with decreasing EP. Thus, decreasing EP was associated with a loss or shrinkage of large diameter auditory nerve fibre dendrites and a reduction of the size of spiral ganglion cells.

Rüttiger et al. (2007) found an age dependent reduction of BDNF mRNA expression in high frequency spiral ganglion cells. In contrast, BDNF protein expression was preserved in the cochlear ganglion cells of old gerbils but declined in their central and peripheral processes.

### **3.7 The endocochlear potential and pathology related to endolymph homeostasis**

The sensitivity of the mechano-electrical transduction by hair cells in the mammalian cochlea depends on the endocochlear potential (EP) in scala media (Wangemann, 2006). The positive EP (80-100 mV) together with the negative intracellular potential of hair cells is the driving force (battery) of sensory transduction. The important contribution of the EP to the sensitivity of the cochlea was demonstrated in experiments, where a reduction of the endocochlear potential by the application of furosemide was associated with threshold shifts in single auditory nerve fibres in cat (Sewell, 1984).

#### **3.7.1 Age-dependent loss of the endocochlear potential**

Several studies in gerbils have shown that the EP, on average, declines with age and inter-animal variability of the EP in old gerbils becomes much higher compared to young gerbils (Gratton et al., 1996, 1997a; Schmiedt, 1983, 1996; Schulte & Schmiedt, 1992). The EP in young gerbils (Schmiedt, 1983) was highest at the base, determined through the round window (92 mV), and slightly lower at more apical locations (76-81 mV); the reduction of the mean EP determined in 3 year old gerbils relative to the means obtained in young gerbils was more pronounced at the base (40 kHz region: 31 mV) and the apex (0.5 kHz region: 27 mV) as compared to the intermediate parts of the cochlea (2 kHz region: 19 mV; 16 kHz region: 23 mV). The loss of the EP and threshold shifts in old gerbils were not related to each other in a direct and simple way. The pattern of CAP threshold shift from low to high frequencies differed from the pattern of EP loss. In addition, the plots of CAP threshold shift as a function of EP shift (Schmiedt, 1983) demonstrate no correlation for young and 30 month old gerbils, despite a variation of the EP over a 40-60 mV range. Only the data from 3 year old gerbils indicated some correlation between CAP threshold and EP, although the scatter in the data was large. Overall, a linear regression analysis suggested that the variation of EP in 3 year old gerbils accounts for 31% of the variation in CAP thresholds (Schmiedt, 1983). The reduction of the mean EP was not associated with a mean loss of potassium concentration in the endolymph of old gerbils and the "effects of age are primarily on EP generation, and not on the chemical potential of  $K_e^{+}$ " between endolymph and perilymph (Schmiedt, 1996).

#### **3.7.2 Histological changes in the stria vascularis and the spiral ligament**

The stria vascularis (SV) plays a central role in the generation of the EP (Wangemann, 2006). Age-dependent changes in the microvasculature that might lead to ischemia and affect SV

function have been the focus of several studies (Gratton & Schulte, 1995; Gratton et al., 1996, 1997b; Sakaguchi et al., 1997a, 1997b; Thomopoulos et al., 1997). Gratton & Schulte (1995) described small regions at the apical and basal ends of the SV that were devoid of capillaries in gerbils as young as 5-10 months. With increasing age, loss of capillaries progressed from both ends towards the middle of the cochlea. Gerbils older than 33 months showed a normal pattern of strial vascularisation only in the mid-region of the cochlea. In the regions of capillary loss, strial atrophy was observed with missing marginal cells and "clumps of pigment" in remaining cells. Gratton et al. (1996) found a significant correlation between the proportion of the SV with normal vascularisation and the EP. However, due to the large inter-animal variability of both parameters, the correlation coefficient indicated that SV pathology explained only up to 37% of the EP variation.

In addition to loss of vascularisation and atrophy of the SV, different types of fibrocytes in the spiral ligament of old gerbils are also affected. Spicer & Schulte (2002) suggested that vacuolisation of type II fibrocytes in regions of old cochleae that show no strial atrophy can be regarded as an early event in the development of strial pathology. Regions with apoptotic or necrotic type II fibrocytes were associated with moderate degeneration of SV, while regions with a complete absence of type II fibrocytes showed advanced SV atrophy. Also, type IV and V fibrocytes showed vacuolisation in old gerbils, while type I fibrocytes did not. Thus, vacuolisation was found in Na,K-ATPase positive fibrocyte types II, IV and V, but not in negative type I fibrocytes. Unfortunately the hearing status was not known and could not be directly correlated with the degree of structural changes in these specimen. Based on their data, Spicer & Schulte (2002) put forward the hypothesis that, within the potassium recycling pathway, impaired secretion of potassium into the endolymph by strial marginal cells could reduce the flow of potassium towards the stria and lead to potassium accumulation and the development of vacuoles in Na,K-ATPase positive fibrocytes. They proposed that dysfunction of marginal cells is the first step leading to fibrocyte pathology and strial degeneration.

### **3.7.3 Changes in enzymes regulating potassium homeostasis**

Spicer et al. (1997) compared the Na,K-ATPase-immunoreactivity (an ion exchange enzyme that uses ATP to pump 3 sodium ions out of the cell in exchange for 2 potassium ions that are pumped into the cell) in the lateral wall and SV of young and old gerbils. Immunostaining in cochleae of old gerbils was more variable than in young gerbils. Old animals showed strial atrophy and no Na,K-ATPase immunoreactivity at the apex, best preservation of SV and immunoreactivity in the middle, and atrophy of SV and loss of immunoreactivity at the base of the cochlea. Immunoreactivity in type II, IV and V fibrocytes of old gerbils decreased less than expression in the adjacent SV, although complete SV degeneration was also associated with loss of immunoreactivity in fibrocytes. The observation that a loss of Na,K-ATPase immunoreactivity in fibrocytes of the spiral ligament appeared to lag behind the loss of staining in the SV supports the suggestion that changes in fibrocytes occur secondarily to alterations in the SV. Sakaguchi et al. (1998) found that age-dependent changes in the expression of the Na-K-Cl co-transporter closely paralleled those reported for the Na,K-ATPase.

Schulte & Schmiedt (1992) determined the Na,K-ATPase immunoreactive volume of the SV from immunostained cochlear sections. A plot of the EP as a function of the normalised SV



volume showed a group of 4 old gerbils with an EP below 20 mV where the SV volume was reduced by more than 70%. In another group of 9 old gerbils, EP varied between 50 and 80 mV with an associated loss of the SV volume between 20% and 70%. Thus, a reduction of the SV volume expressing Na,K-ATPase by up to 70% was associated with only a small loss of the EP. Only when the loss of Na,K-ATPase expressing SV volume increased beyond 70% did the EP show an abrupt break down: the EP appeared tolerant to a relatively large loss of Na,K-ATPase. Consistent with a mean reduction of the Na,K-ATPase immunoreactive volume of SV, the activity of this enzyme was reduced in the lateral wall of old as compared to young gerbils (Gratton et al., 1995) and a low level of Na,K-ATPase activity was associated with a low EP (Gratton et al., 1997b).

Spicer & Schulte (1998) proposed a medial pathway for the recycling of potassium released by inner hair cells. In old gerbils, in contrast to the SV and the lateral wall, fibrocytes of the spiral limbus showed unaltered or upregulated Na,K-ATPase immunoreactivity. In addition, interdental cells remained immunoreactive in cochleae with SV atrophy. Based on these observations, Spicer & Schulte (1998) suggested a normal function of inner hair cells in old gerbils with strial atrophy (although the hearing status of the specimen they analysed was not known). Potassium released by inner hair cells can be recycled into the endolymph by the medial pathway via the remaining Na,K-ATPase immunoreactive limbal fibrocytes and interdental cells.

### **3.8 The gerbil as a model of strial or metabolic presbycusis**

The data discussed above describe a wide range of age-dependent pathologies of the gerbil cochlea. In summary, they suggest that loss of EP due to pathology of the SV and the lateral wall are the main factors that contribute to the threshold shifts observed in auditory nerve fibres and the CAP in old gerbils. This pattern resembles the category of strial atrophy in humans (Schuknecht & Gacek, 1993).

The loss of sensitivity was most pronounced at the tip of single-fibre tuning curves (Schmiedt et al., 1990) and in masked CAP tuning curves (Hellstrom & Schmiedt, 1996) of old gerbils and led to a decreased tip-to-tail ratio of the tuning curves. These changes are similar to the effects of a reduced EP on single-fibre tuning curves in cat (Sewell, 1984). Consequently, Hellstrom & Schmiedt (1996) proposed that “the quiet-aged gerbil can be used as a model for an intact hair-cell system coupled to a chronically lowered EP”. This view was supported by a subsequent study where changes of cochlear function due to a reduction of the EP by chronic furosemide application to the round window in young gerbils resembled those found in quiet-aged, old gerbils (Lang et al., 2010). Schmiedt (1983) proposed the “dead battery theory” and reported that increasing the EP by current injection into scala media in an old animal with an initial EP of 41 mV was associated with increased CAP amplitude and a 20 dB reduction of CAP threshold.

In summary, cochlear sensitivity in quiet-aged gerbils declines on average with a high degree of inter-animal variability. The loss of EP due to degeneration of the SV appears to be the main reason for decreased sensitivity in old gerbils, while loss of hair cells and auditory nerve fibres appear less important. Consequently, gerbils are a useful model of human strial or metabolic cochlear presbycusis.

## 4. The auditory brainstem nuclei

An overview of the auditory pathway is summarised in Strutz (1991) and Schwartz (1991). The central processes of the auditory nerve fibres enter the brain through the internal auditory meatus. Each fibre bifurcates when it enters the cochlear nucleus and sends an ascending branch to the antero-ventral (AVCN) and a descending branch through the postero-ventral (PVCN) to the dorsal (DCN) cochlear nucleus. All auditory nerve fibres terminate in the cochlear nucleus. Neurons of the ventral cochlear nucleus (VCN) predominantly project to the ipsi- and contra-lateral nuclei of the superior olivary complex. The neurons of the DCN project primarily to the contra-lateral, and to a lesser degree, to the ipsi-lateral inferior colliculus (IC). The medial nucleus of the trapezoid body (MNTB) receives input from the contra-lateral VCN and projects primarily to the ipsi-lateral medial (MSO) and lateral (LSO) nuclei of the superior olive. MSO and LSO also receive input from the ipsi- and contra-lateral VCN. MSO neurons project almost exclusively to the ipsi-lateral IC and send collaterals to the dorsal nucleus of the lateral lemniscus. The LSO projects to the ipsi- and contra-lateral IC.

### 4.1 The auditory brainstem response (ABR)

The auditory brainstem response (ABR), recorded from needle electrodes placed behind the ear and the vertex, reflects the synchronised neural activity to the onset of a stimulus. It is less invasive than single-fibre and CAP recordings for evaluating hearing status. Short tone-pips elicit a typical ABR waveform in gerbils with peaks occurring at characteristic latencies. They have been termed i (1-2 ms), ii-iii (2-3.5 ms) and iv (4-5 ms) and can be homologised with the human ABR waves I (generated by the auditory nerve), III (generated by the cochlear nucleus or the MNTB) and V (generated by the lateral lemniscus and IC; Boettcher et al., 1993a).

#### 4.1.1 Age-dependent changes of ABR thresholds

Age-related hearing loss in gerbils was first reported by Henry et al. (1980), showing 15-20 dB threshold elevation for frequencies between 1 and 32 kHz in 2 year old as compared to 3 month old gerbils. Mills et al. (1990) derived ABR thresholds for gerbils between 8 and 36 months of age that were raised in a low-noise environment. Thresholds in 3 year old gerbils varied over a wide range; some old animals showed no or only small threshold elevation compared to young controls, while some old gerbils had more than 50 dB hearing loss. Hearing loss was less than 10 dB in a group of 19 month old gerbils, increased to 10-20 dB at 2 years and further progressed with age. Mean threshold shift at 3 years was approximately 20 dB for the 1-4 kHz range and 25-30 dB for higher frequencies. Threshold shift determined by ABR and CAP measurements in 3 year old gerbils showed a good correspondence.

#### 4.1.2 Age-dependent changes of ABR growth functions

Boettcher et al. (1993a) compared wave ii-iii and wave iv ABR input-output functions of young and old gerbils. The plots of wave ii-iii and iv amplitude as a function of the tone pip level showed a reduction in old as compared to young gerbils that was not directly related to threshold. This was seen through the response amplitude of the best old gerbils with near normal thresholds being greatly reduced at high stimulus levels, especially for the lower test

frequencies. The reduction in response amplitude to high stimulus levels was more pronounced at lower test frequencies, while ABR threshold elevation was more pronounced at the higher test frequencies. As a consequence of the reduced ABR response amplitudes, the slopes of the ABR growth functions were also reduced in old gerbils. Boettcher et al. (1993a) discussed that a loss of spiral ganglion cells could lead to a similar reduction in CAP and ABR amplitudes. However, Keithley et al. (1989) reported a significant reduction in spiral ganglion cell density only for the most basal portion of the cochlea (20 kHz region), while the reduction of ABR response amplitude in old gerbils appeared more pronounced at frequencies  $\leq 4$  kHz. In addition to ganglion cell loss, ABR response amplitude may be affected by a reduction of the EP or a reduction in the degree of synchronisation of the response across the population of auditory neurons. The reduction of ABR amplitude was prominent in old gerbils and largely independent of threshold elevation (Boettcher, 2002a).

#### **4.1.3 Age-dependent changes of ABR response latencies**

Boettcher et al. (1993b) compared wave i, ii and iv response latency between young and old gerbils with different degrees of threshold shift. In the group of normal hearing old gerbils, they found no increase in response latency. Instead, response latency appeared reduced at 8 and 16 kHz for wave i and ii and at all frequencies for wave iv. The reduction was small for wave i and increased for wave iv, resulting in reduced i-iv intervals in normal hearing old as compared to young gerbils. In gerbils with hearing loss, ABR latencies were prolonged at low stimulus levels and normal at high stimulus levels for wave i and ii. Response latency for wave iv in old gerbils with hearing loss was increased for all stimulus levels at 1 and 2 kHz and appeared normal at higher frequencies. Boettcher et al. (1993b) suggested that the decreasing latency along the auditory pathway in normal hearing old gerbils does not reflect changes originating in the periphery, but could rather reflect age-dependent changes in the central auditory system (e.g. loss of inhibition).

#### **4.1.4 The effect of low- and high-pass maskers on ABR thresholds**

ABR measurements have also been used to characterise masking of the response to tone pips by continuous low-pass ( $< 1$  kHz) and high-pass ( $> 8$  kHz) noise-maskers presented at an overall level of 80 dB SPL in young and old gerbils (Boettcher et al. 1995). Threshold shifts for the high-pass masker were similar for young and old gerbils. The shift of the quiet threshold in old gerbils was correlated with the shift of the masked threshold (relative to the mean quiet and masked threshold of young gerbils respectively) for 2 kHz and 4 kHz. For the low-pass masker, old gerbils, especially those with low ABR thresholds in the quiet condition, showed excessive masking compared to young gerbils. Threshold shift in old gerbils in the quiet condition was not correlated with the shift in the presence of the low-pass masker. These data suggest excess upward spread of masking in old as compared to young gerbils: the low-pass masker affected or spread to more basal (higher frequency) cochlear regions in old gerbils, even when ABR thresholds in quiet were near normal.

#### **4.1.5 The interaction of age and acoustic trauma analysed by ABR thresholds**

The interaction of noise-induced and age-dependent hearing loss has been analysed by ABR threshold measurements in gerbils (Boettcher, 2002b; Mills et al., 1997). Anaesthetised

gerbils were exposed monaurally to a 3.5 kHz tone with 113 dB SPL for 1 hour. Pilot experiments had shown that this exposure was associated with a permanent threshold shift around 20 dB in the 4-8 kHz region (Mills et al., 1997).

In the first study (Mills et al., 1997), pre-exposure thresholds for both ears were determined in 18 month old gerbils. Thresholds for the exposed and the non-exposed ears were re-evaluated six weeks (age 19-20 months) after the exposure and at an age of 3 years. Pre-exposure thresholds at the age of 18 months were similar for both ears. Six weeks following the exposure, thresholds of the unexposed ears were similar to pre-exposure thresholds while thresholds of the exposed ears were clearly elevated at 4 and 8 kHz. Comparing the pre-exposure thresholds determined at an age of 18 months and thresholds at 3 years of age for the unexposed ears in this sample showed a relatively small age-dependent increase of 10-13 dB across the whole frequency range (this sample had excellent high frequency hearing compared to data previously presented in Mills et al., 1990). The threshold difference between exposed and unexposed ears was 15 and 12 dB for 4 kHz and 8 kHz 6 weeks following exposure and decreased to 11 and 6 dB in 3 year old gerbils. The additional age-dependent threshold loss in the exposed ear was smaller than in the unexposed ear.

In the second study (Boettcher, 2002b), ABR thresholds were determined for groups of 6-8 and 34-38 month old gerbils before and 30 days following sound exposure to evaluate the effect of age on the susceptibility to acoustic trauma. Pre-exposure thresholds of the 17 old gerbils in this study were exceptionally low, and were only 5-9 dB higher than pre-exposure thresholds of 17 young gerbils across the frequency range tested. Threshold shift (elevation above pre-exposure threshold) induced by the sound exposure was very similar for both age groups below 16 kHz. It was 6 dB or less at 1 and 2 kHz and 15-18 dB at 4 and 8 kHz. Only at 16 kHz was the threshold loss in old gerbils (17dB) higher than in young (9 dB) gerbils. Thus, except for the high frequency region, susceptibility to acoustic trauma in relatively normal hearing old gerbils was not higher than in young gerbils.

#### **4.1.6 ABR and CAP for characterising auditory temporal resolution**

Boettcher et al. (1996) analysed the CAP and ABR responses to two successive 50 ms broadband noise pulses at 60 and 80 dB SPL as a function of the time interval (gap; 2, 4, 8, 16 and 32 ms) between the two noise pulses in young and old gerbils. This design corresponds to the gap detection paradigm in psychoacoustic studies, where the duration of the smallest detectable gap is used as a measure of auditory temporal resolution. The CAP and ABR analysis compared the onset responses to the first and second noise pulse as a function of gap duration. ABR thresholds for tone pips between 1 and 16 kHz were elevated by 10-15 dB in the group of 10 old (33-38 months) as compared to 9 young (4-8 months) gerbils, indicating only a moderate degree of peripheral hearing loss. Consistent with previous CAP (Hellstrom & Schmiedt, 1990) and ABR (Boettcher et al., 1993a) studies, the amplitudes of the potentials evoked by the noise bursts were reduced in old gerbils. In both age groups, the response amplitude to the onset of the second noise pulse decreased with decreasing gap duration, while the response amplitude to the first pulse was independent of gap duration. To compare the recovery of the response with increasing gap duration between the two age groups, despite the reduced response amplitude in old gerbils, the ratio of the response to the second burst divided by the response to the first burst was used. The ratio was smallest for the 2 ms gap duration. For the CAP, the response to the onset of the second

noise pulse for the 32 ms gap had not fully recovered and the ratio was around 0.6 in young and old gerbils. Recovery of ABR wave ii and iv functions with increasing gap duration was more complete as compared to the CAP in young and old gerbils. The comparison of amplitude ratio as a function of gap duration showed no clear systematic difference between both age groups. Thus, despite an absolute difference of response amplitude, the recovery of the response amplitude to the second noise burst with increasing gap duration was similar in young and old gerbils.

The latency for the first noise pulse in the CAP and ABR responses was very similar in young and old gerbils, despite the elevated ABR thresholds to tone pips and the reduced response amplitudes in old gerbils. For the CAP, response latency to the second noise pulse was very similar in old and young gerbils and showed only a small decrease ( $\approx 0.1$  ms) with increasing gap duration. In contrast to the CAP, response latency to the second noise burst showed a higher degree of variation with gap duration for wave ii ( $> 0.2$  ms) and for wave iv ( $> 0.28$  ms). Compared to young gerbils, the response latency of ABR wave ii was elevated for the 2 ms gap and that of wave iv for the 2 and 4 ms gaps in old gerbils. The variation of response latency as a function of gap duration did not differ between young and old gerbils for the CAP. Thus, while response latencies at the level of the cochlea (CAP) did not differ between age groups, the elevated latencies for short gaps in the ABR response (most pronounced for wave iv) argue for altered processing at the brainstem level that is not related to peripheral deficits. Boettcher et al. (1996) proposed that the latency shifts at the level of the brainstem without corresponding shifts in the periphery could be related to a loss of inhibition in the central auditory pathway of aged subjects.

## 4.2 Structural changes

“Healthy” ageing is associated with shrinkage of the brain that is predominantly due to shrinkage of neurons, loss of synapses, reduction of synaptic spines, reduction of the length of myelinated axons and, to a lesser degree, loss of neurons (Fjell & Walhovd, 2010). The pattern of age-dependent structural changes varies greatly between different brain regions. In the following, we will present data on age-dependent changes of auditory brainstem nuclei in the gerbil.

### 4.2.1 The cochlear nucleus (CN)

Spongiform lesions begin to develop in the CN of young gerbils at the age of a few weeks or months and increase in size and number as the gerbil reaches 1-2 years of age (Czibulka & Schwartz, 1991; McGinn & Faddis, 1987; Ostapoff & Morrest, 1989; Statler et al., 1990). Lesions first become prominent in the PVCN and auditory nerve root and can spread to the deep layer of DCN and the caudal region of AVCN. In 1-2 year old gerbils, microcysts also developed in the superior olive, including LSO, the lateral lemniscus and ventral IC, while other non-auditory regions of the brain remained free of lesions (Ostapoff & Morest, 1989). Using immunostaining with antibodies against GFAP and S100, Czibulka & Schwartz (1993) concluded that up to 80% of the microcysts arise from astrocytes and only few lesions occur in dendrites or axons. In contrast, based on ultrastructural analysis and immunostaining with antibodies to MAP2, GFAP and S100, Faddis & McGinn (1997) concluded that their data “did not support a major role for astrocytes in lesion formation”, and transmission

electron microscopy revealed only 8% of the lesions in association with myelinated axons. Thus the contribution of glia and neurons to the formation of microcysts is currently not resolved.

McGinn & Faddis (1987) showed that ligation of the external auditory ear canal in 12 day old gerbils before the onset of hearing suppressed the development of the lesions. Gerbils kept in acoustic isolation between 1 and 3 months of age developed fewer lesions compared to controls exposed to 74-80 dB ambient noise (McGinn et al., 1990). Czibulka & Schwartz (1991) found that the number and size of microcysts decreased between 1 and 3 years of age and the degree of lesions in old gerbils was related to hearing status: the number and the size of lesions were largest in the normal hearing old gerbils, while hearing loss was associated with smaller and fewer lesions. Thus, the activity of auditory nerve fibres terminating in the CN is an important factor for the formation of spongiform lesions and it has been suggested that lesions may be the result of excitotoxicity due to transmitter release by the auditory nerve fibres (Czibulka & Schwartz, 1991; McGinn et al., 1990; Faddis & McGinn, 1997). However, it remains an enigma why lesions are prominent in PVCN, yet typically spare AVCN, which also receives massive input from auditory nerve fibres. Possible functional consequences of spongiform lesions in old gerbils are not yet known.

In addition to spongiform lesions, evidence for neuronal degeneration in the CN was observed by electron microscopy (Ostapoff & Morest, 1989) and through use of aminocupric silver impregnation (McGinn & Faddis, 1998). Czibulka & Schwartz (1991) found a significant reduction in the size of PVCN neurons, but no significant reduction in the number of neurons in the PVCN of gerbils between the age of 1 and 3 years. Ostapoff & Morest (1989) argued that at most 5-6% of the PVCN neurons may be lost due to microcysts. Thus, these studies suggest that age is not associated with a prominent loss of neurons in PVCN.

The cross sectional area of DCN, PVCN and AVCN was determined for 11 young and 18 old gerbils in sections at defined positions along the rostro-caudal extension of the CN (Stehle, 2010; Gleich et al., 2007c). Comparing the group means of young and old gerbils revealed a significant reduction of the cross-sectional area by 12% in old as compared to young gerbils only for AVCN. The data showed a much higher inter-animal variability of AVCN cross-sectional area in old as compared to young gerbils. A subgroup of 8 old gerbils had cross-sectional areas below those from young gerbils (representing an average reduction of almost 25%) while cross-sectional area of the other 10 old gerbils varied within the range observed for young gerbils. Counts of the GABA- and glycine-immunoreactive neurons in the CN subdivisions (Stangl et al., 2009) revealed only for the GABAergic neurons in the AVCN a significant reduction (mean 35%) in old as compared to young gerbils. The analysis of the size (cross sectional area) of inhibitory neurons as a function of age showed only for GABAergic cells of the PVCN a significant reduction (mean 16%) in old gerbils. These data demonstrate distinct and specific age-dependent changes in the CN subdivisions of the gerbil. The shrinkage of AVCN (presumably due to a loss of neuropil) in approximately half of the old gerbils was not associated with a comparable shrinkage in DCN and PVCN. A loss of GABAergic cells was only observed for AVCN, while the size of GABAergic cells was only reduced in the PVCN of old gerbils. Presently, the functional consequences of these structural age-dependent changes in the CN of old gerbils are unknown.

#### **4.2.2 The medial nucleus of the trapezoid body (MNTB)**

The neurons of the MNTB are glycinergic. They convert the excitatory input from the contra-lateral VCN to inhibitory glycinergic projections predominantly to MSO and LSO. A light microscopic analysis of glycine immunoreacted sections showed that spongiform lesions, like those previously described for the CN, were very prominent in the MNTB of 3 year old gerbils, but were almost absent in 1 year old gerbils (Gleich & Strutz, 2002). Thus, spongiform lesions in MNTB develop with a delay of approximately 1-2 years compared to the CN. Spongiform lesions in old gerbils showed a gradient along the MNTB, decreasing from caudal towards rostral. The volume of MNTB was independent of age, as there was no shrinkage of the MNTB in old gerbils. In addition, there was no significant loss of glycinergic neurons in old as compared to young gerbils. In young and old gerbils, there was a systematic gradient of MNTB neuron size: MNTB neurons were largest in the ventro-lateral and smallest in the dorso-medial part of MNTB. According to the tonotopic organisation of MNTB, low-frequency neurons appeared larger on average than high-frequency neurons. Comparing soma size of young and old gerbils revealed a homogenous reduction of cross-sectional area by approximately 20% throughout the MNTB in old gerbils, without any indication that the shrinkage of neurons varied with the tonotopic organisation of MNTB. The reduced size of MNTB neurons in old gerbils may lead to a reduced glycinergic input into MSO and LSO (and other nuclei receiving input from MNTB) and consequently affect processing of binaural stimuli.

#### **4.2.3 The lateral superior olive (LSO)**

The light microscopic analysis of GABA and glycine immunostained sections through the LSO in gerbils revealed that this nucleus was rather resistant to age-dependent changes (Gleich et al., 2004). Although Ostapoff & Morest (1989) had reported the presence of microcysts in the LSO of 1-2 year old gerbils, we found no or only small lesions in the LSO of 7 gerbils over 3 years of age. Only 4 old gerbils showed more-prominent lesions that were mainly restricted to the medial (high frequency) limb of LSO, although all 11 old gerbils in this sample had prominent lesions in the MNTB. Thus, LSO appeared more resistant to the formation of spongiform lesions than the MNTB. Neither the rostro-caudal extension, nor the cross-sectional area of LSO varied with age, demonstrating that the LSO did not shrink in old gerbils. In addition, the number of neurons in Nissl stained sections, as well as the number of GABA- and glycine-immunoreactive neurons did not change with age: there was no loss of neurons in the LSO of old gerbils. The density of inhibitory neurons showed the same gradient along the tonotopic representation of the LSO in young and old gerbils: GABAergic and glycinergic neurons were more prominent in the low as compared to the high-frequency limb. The comparison of the size of inhibitory neurons revealed that the cross sectional area of GABAergic and glycinergic LSO neurons was not affected by age in the lateral low-frequency limb, while there was a significant reduction ( $\approx 30\%$ ) in the medial high-frequency limb. Overall, the LSO showed only limited age-related changes that were restricted to the high-frequency limb.

#### **4.2.4 The medial superior olive (MSO)**

The neurons of the MSO do not express GABA or glycine, but MSO was well recognised in sections through the gerbil brainstem that were immunostained with antibodies against

GABA and glycine (Dalles, 2009, Gleich, 2006; 2007). The number of MSO neurons was independent of age: there was no loss of MSO neurons in old gerbils. However, the cross sectional area of MSO neurons and the cross sectional area of MSO both decreased by 10% and 20% respectively in old as compared to young gerbils. The shrinkage of MSO in old gerbils is a combination of the shrinkage of MSO neurons and a reduction in the innervation density of MSO (loss of neuropil). Age-dependent structural changes in the gerbil MSO were quite pronounced.

#### **4.2.5 The inferior colliculus (IC)**

The analysis of age-dependent changes of the gerbil IC (Gleich et al., 2011) revealed a significant shrinkage of the IC cross-sectional area (13%) in old as compared to young gerbils. Although the mean number and cross-sectional areas of GABAergic cells in the IC were slightly smaller in old as compared to young gerbils, the difference between both groups was not significant in the sample of 7 young and 18 old gerbils analysed. The age-dependent changes in the GABAergic system of the gerbil IC appeared less pronounced than those previously described in rat (Caspary et al., 1995). This might be explained by differences in the degree of peripheral hearing loss of old rats and gerbils.

#### **4.2.6 Variation of age-dependent structural changes between auditory nuclei and potential functional consequences**

The structural changes in the different auditory nuclei discussed above (loss of neurons, shrinkage of neurons and shrinkage of the whole nucleus due to loss of innervation) vary considerably. The effect of age appeared least in DCN and LSO and most for AVCN and MSO. Unfortunately, the functional consequences of the age-dependent structural changes in a specific nucleus on auditory processing are typically not well understood except for MSO and LSO, where it has been shown that they process two distinct aspects of binaural sound analysis: MSO analyses inter-aural time differences while LSO analyses inter-aural level differences (see review in Irvine, 1992), two separate cues that can be used for localisation or lateralisation of a sound source. The limited age-dependent pathology in LSO and the more pronounced pathology of MSO suggest that lateralisation of a sound source in old gerbils should be less affected when based on inter-aural level difference and more affected when based on inter-aural time difference. Unfortunately, behavioural data in gerbils addressing this question are not available. However, Babkoff et al. (2002) showed that for a sample of 78 human subjects aged 21-88 years, tested by the presentation of click trains via head phones, lateralisation based on inter-aural level difference did not change with age while the inter-aural time difference for correct lateralisation increased with age. The correlation of the degree of age-dependent structural changes in LSO and MSO of the gerbil and the effect of age on lateralisation based on inter-aural level- and inter-aural time-difference in humans is an example for a potential causal relationship of structural and functional age-dependent pathology.

### **5. Psychoacoustic / behavioural measurements**

The first behavioural audiogram of the gerbil was determined by Ryan (1976) using a shock avoidance procedure. Subsequently, Sinnott et al. (1997) developed a go-nogo procedure



where gerbils initiate a test trial by jumping onto an observation platform and indicate the perception of the test stimulus by jumping off the platform. In this procedure, correct responses are rewarded by a small food pellet. By repeated presentation of a fixed set of test stimuli, where the parameter under investigation varies over a given range (e.g. sound pressure level), a psychometric function is constructed by plotting the correct response probability as a function of the stimulus parameter. The derivation of threshold and other parameters from psychometric functions of gerbils are described in detail in Gleich et al. (2006). In addition to measuring threshold for the detection of signals in quiet, more complex tasks require the detection of a stimulus that deviates from a constantly and repeatedly presented background stimulus. This approach has been used to characterise the ability to discriminate between synthetic speech-like stimuli (Sinnott & Mosqueda, 2003), determine the minimum audible gap duration in a broadband noise pulse (Hamann et al., 2004) and characterise forward masking (Gleich et al., 2007a) in gerbils.

### 5.1 The audiogram and age-dependent threshold elevation

Behaviourally-determined thresholds in up to 3-year-old gerbils using positive reinforcement (food reward; Hamann et al., 2002) resembled those previously reported by Ryan (1976) using shock avoidance. Behavioural thresholds of 30-36 month-old gerbils showed no significant elevation for broadband noise and 10 kHz and only a small degree of hearing loss at 2 kHz (mean 7.2 dB) compared to gerbils up to 1 year of age. Inter-animal variability of behavioural thresholds in gerbils older than 3 years increased and showed a higher mean loss. However, in clinical terms, the losses were only mild, typically less than 40 dB (Hamann et al., 2002). This pattern differed considerably from the description of hearing loss based on previous CAP and ABR measurements where the mean hearing loss was 10-20 dB at 2 years of age and increased to 25-30 dB for frequencies above 4 kHz in 3 year old gerbils (Hellstrom & Schmiedt, 1990; Mills et al., 1990). To address the question whether the different patterns of hearing loss observed by ABR and behavioural testing were due to methodology or the breeding line, Hamann et al. (2002) determined ABR thresholds in a group of 5 gerbils at the age of 28-29 months. On average, these gerbils showed a 14 dB hearing loss, whereas thresholds in 4 of these gerbils determined at 18 months of age were not elevated. Based on the ABR, these 5 gerbils developed more than 10 dB hearing loss between 18 and 28-29 months of age. Behavioural thresholds of these same gerbils were obtained a few months following ABR testing at an age of 31-33 months and were not found to be elevated compared to the behavioural thresholds of young gerbils. Thus, although ABR thresholds were clearly elevated in these gerbils at 28-29 months of age, the behavioural thresholds determined a few months later showed no hearing loss, the elevation of ABR thresholds in these old gerbils was not reflected in the behavioural thresholds. The difference between behavioural thresholds and thresholds determined by ABR in the frequency range of 1-8 kHz increased from 13-14 dB in young (< 12 months) to 25-30 dB in approximately 2 year old gerbils. A similar observation was described in Boettcher (2002a) for humans. The difference between ABR and behavioural thresholds was around 8 dB at 2 and 4 kHz in a group of young human subjects and increased to around 20 dB in a group of old human subjects. Thus, ABR based thresholds in old humans and gerbils may lead to an over-estimation of threshold loss compared to pure tone audiometry.

There is not a simple, straight-forward explanation for the age-dependent, increasing discrepancy between behavioural and ABR thresholds (Hamann et al., 2002). One factor is a decreased synchronisation of the neural responses that will lead to reduced amplitudes of evoked potentials and reduced slopes of the CAP and ABR growth functions. In addition, a specific loss of auditory nerve fibres with low spontaneous activity, that typically have higher thresholds than those with high spontaneous activity could contribute to reduced amplitudes of CAP and ABR without associated elevation of threshold (Schmiedt et al., 1996; Lin et al., 2011). The advanced age-dependent cochlear pathologies discussed above (see heading 3) will eventually lead to behavioural manifestation of hearing loss.

## 5.2 Temporal integration

Thresholds for tones increased by more than 10 dB in both normal hearing, young gerbils and old gerbils, as signal duration was reduced from 300 to 10 ms (Gleich et al., 2007b). Like in humans and other species, temporal integration was reduced in gerbils with hearing loss and varied as a function of threshold elevation.

In the presence of fixed-level modulated and un-modulated speech like maskers, threshold shift due to the masker was inversely related to threshold in quiet: sensitive gerbils showed more masking compared to gerbils with slightly elevated thresholds. Consequently, the temporal integration functions (plots of the masked threshold as a function of duration) became very similar for all 13 gerbils with an age varying between 7 and 43 months and the functions were independent of peripheral hearing. Compared to the unmodulated masker, thresholds for short signals (10 and 30 ms) showed slightly more masking, while those for long signals (300 and 1000 ms) showed slightly less masking in the presence of the modulated masker, suggesting that long signals can be detected in the troughs while detection of short signals interferes with the peaks of the modulated masker. These data suggest that temporal integration in normal hearing gerbils is not affected by age.

## 5.3 Gap detection

The gap detection paradigm determines the minimum duration for the detection of a short period of silence (gap) embedded in a broadband noise pulse. It has been widely used to characterise the temporal resolution of the auditory system. By selecting old human subjects with no or minimal peripheral hearing loss (determined by pure tone audiometry), Snell (1997) demonstrated that mean gap detection thresholds increased with age even in the absence of peripheral hearing loss: some old subjects showed impaired performance, while others retained good temporal resolution, resulting in an increased inter-individual variability of gap detection thresholds in old human subjects. Very similar results were obtained in gerbils (Hamann et al., 2004). When tested with a noise carrier presented 30 dB above the threshold for the carrier, the minimum audible gap in young gerbils was below 4 ms, while approximately 50% of the old gerbils had gap detection thresholds above 4 ms. The variation of the threshold for the noise carrier explained less than 20% of the variation of the gap detection threshold in gerbils. This suggests that peripheral hearing loss was not the dominant cause of impaired temporal resolution. These data point to central auditory processing deficits that result in increased gap detection thresholds in normal hearing old humans and gerbils and are consistent with results obtained by ABR in gerbils (Boettcher et

al., 1996). The similarity of age-dependent changes in gap detection by humans and gerbils emphasises the usefulness of the gerbil model for the analysis of impaired auditory temporal processing.

#### **5.4 Forward masking**

Forward masking is a phenomenon through which threshold for a probe that follows a signal (masker) is elevated (masked) and recovers with time ( $\approx 100$  ms) following the end of the masker. Increased masking and delayed recovery from preceding acoustic stimulation interferes with the detection of fluctuations and transients in sound signals and might contribute to age-dependent impairment of speech perception. In the analysis of the effect of age on forward masking in gerbils (Gleich et al., 2007a) a 2.85 kHz masker presented at 40 dB SPL and repeated continuously every 1.6 seconds served as a constant background signal. Animals had to detect trials where a short 2.85 kHz probe signal (20 ms) was presented 2.5 ms after the end of the masker. In addition to the masked threshold, the threshold for the probe signal without a masker was determined to characterise peripheral hearing. In a sample of 15 gerbils between 5 and 36 months of age, threshold for the probe in quiet was independent of age (mean 12 dB SPL). These animals showed no sign of peripheral hearing loss. In contrast, the masked thresholds of these gerbils increased from around 33 dB SPL at 1 year of age to 48 dB SPL at an age of 3 years. The efficacy of the masker increased by 15 dB between 1 and 3 years of age. The increased degree of forward masking in old gerbils in the absence of elevated thresholds in the condition without a masker suggests a deficit in central, rather than peripheral, auditory processing. An analysis of forward masking using ABR in humans also demonstrated increased forward masking in old subjects with normal audiometric thresholds and led to the conclusion that this was likely due to changes in central auditory processing (Walton et al., 1999). Thus, gerbils appear to be a useful model for the analysis of the interaction of age and forward masking.

#### **5.5 Auditory spatial resolution**

Age-dependent structural changes in auditory nuclei involved in binaural processing have been discussed above (see headings 4.2.3-4.2.5). Consistent with the pathology in MNTB, MSO and LSO, auditory spatial resolution was impaired in old gerbils (Maier et al., 2008). The minimum resolvable angle in a sound lateralisation task showed a higher degree of inter-animal variability in old (32 to 51 months), as compared to young (3-8 months), gerbils. The angle for pure tones (0.5 and 8 kHz) and narrowband noise centred at 0.5 and 2 kHz was  $\approx 50$ - $60^\circ$  in old gerbils, approximately twice the angle found in young gerbils. Maier et al. (2008) suggest that spongiform lesions in the VCN compromise the excitatory input, while pathology of the MNTB affects the inhibitory input to LSO and MSO and contribute to impaired auditory spatial resolution in old gerbils.

#### **5.6 Pharmacotherapy**

The available data indicate that ageing is associated with a loss of inhibition in the central auditory pathway, which could contribute to impaired auditory temporal processing (Caspary et al., 2008). Age-dependent changes in neurotransmitter systems might be influenced by pharmacotherapy and the similarity of age-dependent deficits between

humans and gerbils with respect to gap detection and forward masking makes the gerbil an ideal model to test the effect of candidate substances on performance. Some anti-convulsive drugs in the context of epilepsy were designed to interact with the GABA system.

For our first study, we chose to analyse the effect of Sabril® (vigabatrin) on gap detection (Gleich et al., 2003). Vigabatrin blocks the GABA converting enzyme GABA transaminase and consequently leads to elevated levels of GABA in the brain. The effect of vigabatrin at a dose of 50 mg/kg/day was dependent on the initial gap detection threshold. Performance in gerbils with initially low gap detection thresholds were not systematically affected by the drug, while those with initially elevated gap detection thresholds improved and normalised to a level comparable to sensitive animals. The beneficial effect of vigabatrin on impaired gap detection was reversible, with gap detection thresholds increasing after the end of the treatment. These data clearly demonstrate the potential use of pharmacotherapy for the treatment of impaired auditory temporal resolution. Unfortunately, severe side effects on the visual system prevent the therapeutic use of vigabatrin for the treatment of hearing loss.

In a subsequent study, we evaluated the effect of gabapentin on gap detection and forward masking in gerbils, since other studies suggested beneficial effects of gabapentin for certain forms of tinnitus (Gleich & Strutz, 2011). Gabapentin was initially designed as a GABA analogue for the treatment of epilepsy and is also used for the treatment of neuropathic pain. In gerbils, gabapentin had no beneficial effect on impaired gap detection or on elevated masked thresholds. Unexpectedly, the data showed that gabapentin at a dose of 350 mg/kg/day increased masked thresholds in young gerbils, while it had no significant effect in old gerbils that had elevated masked thresholds before gabapentin treatment. The lack of a beneficial effect on impaired gap detection and increased forward masking in old gerbils could be due to an insufficient effect of gabapentin on the GABA system, while the increased masked thresholds of young gerbils during gabapentin treatment might be related to its interaction with voltage-gated calcium channels.

## 6. Conclusion

At the level of the cochlea, pathology begins to affect the marginal cells of the stria vascularis and eventually leads to a reduction of the endocochlear potential in old gerbils. Loss of hair cells and loss of auditory nerve fibres and spiral ganglion cells are not major contributors to age-dependent peripheral hearing loss. Consequently, gerbils can be regarded as a good model for strial or metabolic presbycusis.

Behavioural and evoked potential (CAP, ABR) measures of auditory sensitivity are useful to characterise hearing status; however, the degree of age-dependent threshold elevation depends on the method used: the discrepancy between thresholds determined psychoacoustically and by evoked potentials increases with age; evoked potentials indicate more threshold loss than behavioural methods in old gerbils and old humans.

Auditory nuclei in the ascending auditory pathway of gerbils show specific and distinct age-dependent structural changes, where some nuclei appear more affected than others. Structural changes in nuclei involved in binaural processing are associated with impaired auditory spatial resolution in old gerbils. For LSO and MSO, the degree of age-dependent pathology in gerbils can be correlated with age-dependent changes in human performance

in sound lateralisation tasks, which are based on inter-aural level and inter-aural time difference cues. This suggests a causal relationship between structural and functional age-dependent changes.

The age-dependent decline of auditory temporal resolution determined by gap detection and forward masking in gerbils and humans is very similar and probably due to loss of inhibition or age-dependent disturbance of neurotransmitter balance in the auditory pathway. Augmentation of the GABA system by vigabatrin was effective in the treatment of impaired gap detection in gerbils and demonstrates that pharmacotherapy of central auditory processing deficits appears feasible, in principle. The challenge is to identify appropriate substances that act on the disturbed neurotransmitter balance in advanced age. The available data show that the gerbil is a suitable model to evaluate the efficacy of potential therapies for the treatment of impaired central auditory processing.

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## 8. References

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Authored by 17 international researchers and research teams, the book provides up-to-date insights on topics in five different research areas related to normal hearing and deafness. Techniques for assessment of hearing and the appropriateness of the Mongolian gerbil as a model for age-dependent hearing loss in humans are presented. Parental attitudes to childhood deafness and role of early intervention for better treatment of hearing loss are also discussed. Comprehensive details are provided on the role of different environmental insults including injuries in causing deafness. Additionally, many genes involved in hearing loss are reviewed and the genetics of recessively inherited moderate to severe and progressive deafness is covered for the first time. The book also details established and evolving therapies for treatment of deafness.

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