Development of tinnitus-related neuronal hyperactivity through homeostatic plasticity after hearing loss: a computational model

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Abstract
Tinnitus, the perception of a sound in the absence of acoustic stimulation, is often associated with hearing loss. Animal studies indicate that hearing loss through cochlear damage can lead to behavioral signs of tinnitus that are correlated with pathologically increased spontaneous firing rates, or hyperactivity, of neurons in the auditory pathway. Mechanisms that lead to the development of this hyperactivity, however, have remained unclear. We address this question by using a computational model of auditory nerve fibers and downstream auditory neurons. The key idea is that mean firing rates of these neurons are stabilized through a homeostatic plasticity mechanism. This homeostatic compensation can give rise to hyperactivity in the model neurons if the healthy ratio between mean and spontaneous firing rate of the auditory nerve is decreased, for example through a loss of outer hair cells or damage to hair cell stereocilia. Homeostasis can also amplify non-auditory inputs, which then contribute to hyperactivity. Our computational model predicts how appropriate additional acoustic stimulation can reverse the development of such hyperactivity, which could provide a new basis for treatment strategies.

Introduction
It is estimated that 2% of the general population suffer from chronic tinnitus (Pilgramm et al., 1999). The origin of this phantom percept, however, is not well understood, and therefore etiologic treatments are not available. Even though neural correlates of tinnitus have been found in animal studies, mechanisms for its development have not yet been identified.

In humans, tinnitus is often associated with sensorineural hearing loss (Henry et al., 1999). Behavioral studies indicate that animals also experience tinnitus after cochlear damage caused by acoustic trauma (Brozoski et al., 2002; Heffner & Harrington, 2002; Kaltenbach et al., 2004). Such damage to the auditory periphery leads to changes in neural activity in the auditory brainstem (Kaltenbach et al., 1998, 2000; Kaltenbach & Afman, 2000; Brozoski et al., 2002; Kaltenbach et al., 2004), the midbrain (Wang et al., 2002a), and the cortex (Seki & Eggermont, 2002, 2003; Noreña & Eggermont, 2003). Altered activity in the auditory cortex might therefore be a physiological correlate of tinnitus, but possibly not always its origin.

The earliest processing stage in the auditory pathway where tinnitus-related changes have been observed is the dorsal cochlear nucleus (DCN), which receives feedforward input from the auditory nerve (AN). Acoustic trauma leads to increased spontaneous firing rates in the DCN (Kaltenbach et al., 1998, 2000; Kaltenbach & Afman, 2000; Brozoski et al., 2002; Kaltenbach et al., 2004), and the degree to which the spontaneous rates are elevated is related to the strength of the behavioural evidence for tinnitus (Kaltenbach et al., 2004). Such hyperactivity occurs only in those regions of the DCN that are innervated by the lesioned parts of the cochlea (Kaltenbach et al., 2002). These experimental results present a paradoxical situation; cochlear damage leads to an overall decrease of AN activity, but the spontaneous firing rates in the DCN are increased.

Interestingly, hyperactivity in the DCN develops within days after hearing loss (Kaltenbach et al., 1998, 2000). Mechanisms of homeostatic plasticity also operate on this time scale (see, e.g. Turrigiano et al., 1998). Homeostatic plasticity is a response of neurons to sustained changes in their mean activity caused, for example, by changed mean synaptic drive. Homeostasis aims at stabilizing the mean firing rate of a neuron (Turrigiano, 1999; Burrow & Murthy, 2003) by scaling the strength of synapses and altering the intrinsic neuronal excitability (Turrigiano et al., 1998; Desai et al., 1999; Kilman et al., 2002). Such changes have been observed in the auditory cortex and in various regions of the auditory brainstem in response to sensory deprivation by means of cochlear ablation or cochlear damage through acoustic trauma: excitatory synaptic transmission was strengthened (Vale & Sanes, 2002; Muly et al., 2004; Kotak et al., 2005), inhibitory transmission was weakened (Suneja et al., 1998a, 1998b; Vale & Sanes, 2002; Kotak et al., 2005), and excitability was increased (Kotak et al., 2005).

To address the question of how peripheral hearing loss may lead to tinnitus-related hyperactivity of neurons in the auditory brainstem, we utilize a phenomenological model of the responses of AN fibers and downstream auditory neurons, for example in the cochlear nucleus (CN). The computational model is not intended to capture all known physiological details of the AN and the CN in detail. Instead we use a minimal model to demonstrate the basic mechanism of how homeostatic plasticity could contribute to the development of hyperactivity in response to altered input statistics. We therefore, for example, do not model single AN fibers but rather describe how the population firing rate of a group of AN fibers depends on the intensity of acoustic stimuli, and how the rate-intensity function of the population is altered by various kinds of cochlear damage.
We set the mean value

within the dynamic range of AN fibers yield similar results. The linear amplitudes of the sound stimuli (see, e.g. Escabi intensity levels in dB corresponds to a long-tailed distribution of the distribution for all frequencies. This Gaussian distribution of sound

to capture the resulting, broader, intensity distribution of a mixture of vocalizations and 9 dB for environmental sounds (Escabi Standard deviations of 15 dB were reported for speech, 13 dB for this Gaussian distribution so that \( f(I) \) has maximum information on \( I \) if \( I \) is larger than some threshold \( I_{th} \). For \( I > I_{th} \), \( f(I) \) is proportional to the normalized cumulative distribution function of \( p_{th}(I) = \int_{I_{th}}^{I} p_{th}(I') dI' \) (infomax principle, Laughlin, 1981). For high \( I \), \( f(I) \) saturates at rate \( f_{max} \). For \( I < I_{th} \), there is spontaneous activity \( f(I < I_{th}) = f_{sp} \), which occurs with probability: \( P_{sp} = \int_{-\infty}^{0} p_{th}(I) dI \) (see also Fig. 2). To summarize, we have:

\[
f(I) = \begin{cases} f_{sp} & \text{for } I < I_{th}, \\ f_{sp} + (f_{max} - f_{sp}) \frac{I - I_{th}}{I_{max} - I_{th}} & \text{for } I \geq I_{th}. \end{cases}
\]

Due to our infomax assumption, the distribution \( p_{th}(f) \) of AN firing rates is flat for \( f_{sp} < f \leq f_{max} \) and has a delta peak at frequency \( f = f_{sp} \) (see Fig. 3b),

\[
p_{th}(f) = P_{sp} \delta(f - f_{sp}) + \left\{ \begin{array}{ll}
p_a & \text{for } f_{sp} < f \leq f_{max}, \\ 0 & \text{otherwise}. \end{array} \right.
\]

where \( p_a = (1 - P_{sp})/(f_{max} - f_{sp}) \) is the probability density of driven activity. The mean AN firing rate is: \( \langle f \rangle = \int f' p_{th}(f') df' \). Using Eqn (3) we have:

\[
\langle f \rangle = P_{sp} f_{sp} + \int_{f_{sp}}^{f_{max}} f' \cdot p_{th}(f') df'.
\]

The main parameters that influence AN responses in our model equations (Eqs 2, 3, and 4) are the threshold \( I_{th} \), which determines the probability of spontaneous activity, the spontaneous rate \( f_{sp} \), and the maximum rate \( f_{max} \). They are changed by cochlear damage.

We consider the effects of loss of inner and outer hair cells and of damage to the stereocilia of inner and outer hair cells. We denote the fraction of remaining IHCs by \( H_{I} \), the fraction of remaining OHCs by \( H_{O} \), and the fraction of undamaged stereocilia by \( S \). The three parameters \( H_{I}, H_{O}, \text{ and } S \) vary between 1 (healthy) and 0 (loss of all hair cells or damage of all stereocilia). For simplification, we assume that our infomax assumption for the AN population response (see above) also holds in the case of cochlear damage.

The death of an IHC deprives the corresponding AN fibers of their input, because each AN fiber only contacts one IHC, and each IHC is contacted by 10–30 AN fibers (Ryugo, 1992). Moreover, the amplitude of the AN’s compound action potential is reduced approximately proportionally to the amount of IHC loss (Wang et al., 1997; Salvi et al., 2000). We therefore model the effect of IHC loss by a multiplicative reduction of the AN population firing rate. IHC loss then affects the spontaneous firing rate, \( f_{sp}(H_{I}) = H_{I} f_{sp} \), and the

\[f_{th}(I) = \begin{cases} f_{sp} & \text{for } I < I_{th}, \\ f_{sp} + (f_{max} - f_{sp}) \frac{I - I_{th}}{I_{max} - I_{th}} & \text{for } I \geq I_{th}. \end{cases}\]

\[\langle f \rangle = P_{sp} f_{sp} + \int_{f_{sp}}^{f_{max}} f' \cdot p_{th}(f') df' = P_{sp} f_{sp} + \frac{1}{2} (1 - P_{sp}) (f_{max} + f_{sp}).\]
maximum firing rate of the AN, \( f_{\text{max}}(H_o) = H_{I} f_{\text{max}} \) (see Fig. 2a). From Eqn (4) we find the mean AN firing rate after IHC loss,

\[
\langle f(H_o) \rangle = H_{I} \cdot \langle f \rangle.
\]

(5)

OHC loss is approximated by an increase in the AN threshold \( I_{th} \) in proportion to the amount of OHC loss, \( I_{th}(H_o) = I_{th} + \Delta_{o} (1 - H_{o}) \) where \( \Delta_{o} = 60 \text{ dB} \) is the threshold shift for the loss of all outer hair cells at \( H_{o} = 0 \) (Dallos & Harris, 1978; Harrison, 1981). Therefore, the probability of spontaneous firing is increased, \( P_{sp}(H_o) \geq P_{sp} \) where \( P_{sp}(H_o) = \int_{-\infty}^{\infty} f_{sp}(I) \, dI \), and the probability density of driven activity is reduced to \( p_{d}(H_o) = (1 - P_{sp}(H_o))/(f_{\text{max}} - f_{sp}) \). The spontaneous and the maximum discharge rates are not affected (Dallos & Harris, 1978; Schmiedt & Zwislocki, 1980). The resulting response curves for the population firing rate of the AN are steeper, as observed experimentally for single fibers (Harrison, 1981; see Fig. 2b). The mean firing rate is then given by:

\[
\langle f(H_o) \rangle = P_{sp}(H_o) f_{sp} + \frac{1}{2} (1 - P_{sp}(H_o)) (f_{\text{max}} + f_{sp}).
\]

(6)

Noise-induced damage to the stereocilia of inner and outer hair cells increases the response threshold of AN fibers and decreases their spontaneous firing rate (Liberman & Dodds, 1984; Liberman, 1984). For a complete loss of all stereocilia (\( S = 0 \)) the threshold is increased by \( \Delta_{s} = 80 \text{ dB} \), and the spontaneous rate is decreased by a factor of two-thirds (estimates based on Liberman & Dodds, 1984; Liberman, 1984). For intermediate degrees of stereocilia damage (SD) where \( 0 \leq S \leq 1 \), we have \( I_{th}(S) = I_{th} + \Delta_{s} \cdot (1 - S) \), and \( f_{sp}(S) = f_{sp}(1 + 2S)/3 \).

For OHC loss, the probability of spontaneous activity depends on the amount of threshold shift, \( P_{sp}(S) = \int_{-\infty}^{\infty} f_{sp}(I) \, dI \), and the probability density of driven activity is then given by \( p_{d}(S) = 1 - P_{sp}(S) \).

Together with the decrease in spontaneous firing rate, we obtain:

\[
\langle f(S) \rangle = P_{sp}(S) f_{sp}(S) + \frac{1}{2} (1 - P_{sp}(S)) (f_{\text{max}} + f_{sp}(S)).
\]

(7)

for the mean firing rate of the AN after SD.

If IHC and OHC loss, or SD and IHC loss, occur together, we assume that the different types of cochlear damage independently influence the parameters of the AN response function. For IHC and OHC loss, we then get the spontaneous rate \( f_{sp}(H_{I}, H_{o}) = H_{I} f_{sp} \), the maximum rate \( f_{\text{max}}(H_{I}, H_{o}) = H_{I} f_{\text{max}} \), and the threshold \( I_{th}(H_{I}, H_{o}) = I_{th} + \Delta_{o} (1 - H_{o}) \). The mean firing rate of the AN population is:

\[
\langle f(H_{I}, H_{o}) \rangle = H_{I} \cdot \langle f \rangle.
\]

(8)

where \( \langle f(H_o) \rangle \) is given in Eqn (6). Similarly, for IHC loss and SD, we have the spontaneous firing rate \( f_{sp}(H_{I}, S) = H_{I} f_{sp}(S) \), the maximum firing rate \( f_{\text{max}}(H_{I}, S) = H_{I} f_{\text{max}} \), and the threshold \( I_{th}(H_{I}, S) = I_{th} + \Delta_{o} (1 - S) \). The mean AN population rate is

\[
\langle f(H_{I}, S) \rangle = H_{I} \cdot \langle f \rangle.
\]

(9)

where \( \langle f(S) \rangle \) is given in Eqn (7).

**Model for a downstream auditory neuron**

Downstream auditory neurons, for example in the cochlear nucleus, are modelled as firing rate units with some nonlinear response function. Each model neuron receives excitatory input from the AN at a variable rate \( f \), and a constant additional input from other sources at rate \( f_{\text{add}} \). The sum of the two inputs is weighted by the adjustable synaptic gain factor \( g \), and a response threshold \( \theta \) is subtracted. The firing rate \( r \) of the model neuron is then:

\[
r = R(f + f_{\text{add}}) = \begin{cases} 
     r_{\text{high}} \cdot \tanh \left( \frac{(f + f_{\text{add}}) - \theta}{r_{\text{high}}} \right) & \text{for } g \cdot (f + f_{\text{add}}) \geq \theta, \\
     0 & \text{otherwise}, 
\end{cases}
\]

(10)

where \( r_{\text{high}} = 300 \text{ Hz} \) is the highest possible firing rate of the model neuron. The gain factor \( g \) is set to 1 for the initial, healthy condition. The threshold \( \theta \) is set to \( \theta = f_{\text{add}} \) to ensure that in the healthy case (\( g = 1 \)) the model neurons have the same response distribution for different firing rates of the additional input (see Figs 3 and 5). The spontaneous firing rate of the model neuron is \( r_{sp} = R(f_{\text{add}} + f_{\text{add}}) \), and the maximum firing rate is \( r_{max} = R(f_{\text{max}} + f_{\text{add}}) \).

The probability density function \( q(r) \) of the model neuron’s firing rates \( r \) is derived from the distribution \( p_{r}(f) \) of AN responses and the response function \( R \). The probability \( P_{r} \) of spontaneous activity of the model neuron is the same as in the AN. In summary, we have:

\[
q(r) = \frac{1}{R'(R^{-1}(r))} p_{r}(R^{-1}(r)) \\
= P_{sp} \cdot \delta(r - r_{sp}) + \begin{cases} 
     \frac{1}{g} \cdot \frac{1}{1 - (r/r_{\text{high}})^{2}} & \text{for } r_{sp} < r \leq r_{max} \\
     0 & \text{otherwise}.
\end{cases}
\]

(11)

The mean firing rate of the model neuron is then given by:

\[
\langle r \rangle = \int_{r_{sp}}^{r_{max}} r \cdot q(r) \, dr \\
= P_{sp} r_{sp} + \frac{P_{w}}{g} \int_{r_{sp}}^{r_{max}} \frac{r'}{1 - (r'/r_{\text{high}})^{2}} \, dr' \\
= P_{sp} r_{sp} + \frac{P_{w} r_{sp}^{2}}{2g} \ln \frac{r_{\text{high}} - r_{sp}}{r_{\text{high}} - r_{max}},
\]

(12)

where \( r_{sp} \) and \( r_{max} \) depend on \( g \) (see above) so that \( \langle r \rangle \) increases with increasing \( g \).

**Homeostatic plasticity**

Homeostatic plasticity serves to stabilize the mean activity of a neuron around a certain target level over long time scales on the order of days (Turrigiano, 1999; Burrone & Murthy, 2003). We model the effects homeostatic plasticity by a change in the gain factor \( g \) that is triggered by deviations of the mean activity \( \langle r \rangle \) from a certain target rate \( r^{*} \). We assume that the response function \( R \) is not affected by homeostatic plasticity, as in our model the adjustment of \( g \) is sufficient to mimic the changes in effective response gain by homeostatic scaling. The change of \( g \) that is necessary to restore the mean activity \( \langle r \rangle \) in Eqn (12) to its target level \( r^{*} \) is computed numerically. The time-course of homeostatic plasticity is not considered. An upper limit of three (three times the normal gain) is imposed onto \( g \) to reasonably account for physiological constraints on synaptic strengths and excitability (see, e.g. Turrigiano et al., 1998).
**Additional acoustic stimulation**

During the presentation of an acoustic stimulus at a suprathreshold intensity $I_{stim} > I_{th}$, the AN firing rate is $f_{stim} = R(I_{stim})$. If the stimulus is presented continuously, the spontaneous firing rate $f_{sp}$ of the AN fiber population is to be replaced by $f_{stim} > f_{sp}$. The AN then fires at rate $f_{stim}$ with probability $P_{stim} = \int_{I_{stim}}^{\infty} p(I) \, dI$, that is whenever $I_{stim}$ is higher than the intensity $I$ of an environmental stimulus with distribution $p(I)$. The mean firing rate $\langle r \rangle$ of a second-order model neuron can then be calculated using Eqn (12) with $P_{sp}$ and $f_{sp}$ replaced by $P_{stim}$ and $f_{stim}$. If $\langle r \rangle$ differs from the desired value $r^*$, homeostatic plasticity is activated, and $g$ is changed. After homeostasis, the value of $g$ depends also on $I_{stim}$. The required stimulus intensity $I_{stim}$ to reverse hyperactivity (see Fig. 8) is such that $g(I_{stim})$ after homeostasis leads to a normal spontaneous firing rate $r_{sp, healthy}$ in the second-order neuron when the additional stimulation is turned off, namely

$$R(f_{sp} + g(I_{stim}^*)) = r_{sp, healthy}.$$ 

The calculation of $I_{stim}$ is carried out numerically, and separately for each frequency channel.

**Implementation**

The model was implemented using MATLAB from the MathWorks Inc.

**Results**

The aim of this study was to demonstrate how a stabilization of neuronal activity through homeostatic plasticity could contribute to the development of hyperactivity in the auditory system after hearing loss. Figure 1 illustrates how homeostasis stabilizes a neuron’s mean activity. We assume that, initially, some input drives the neuron to fire within a range between its spontaneous and maximum firing rates. The mean firing rate is determined by the statistics of the input signal. Let us focus on a case where after a lesion the statistics of the input changes such that the mean firing rate of the neuron is decreased without affecting the range of firing rates, a scenario that is reminiscent of the loss of outer hair cells in the cochlea. If homeostatic plasticity then restores the mean rate to its target value, for example by increasing synaptic efficacies, this can also increase the neuron’s spontaneous firing rate, thus causing hyperactivity. Hyperactivity typically develops when the activity of the neuron is changed such that the ratio between the mean and spontaneous firing rate is reduced; further details of the activity statistics are not overly important. We now apply this concept to the first stages of the auditory pathway, using a phenomenological model of the responses of AN fibers and downstream auditory neurons in the CN.

**Population firing rate of the auditory nerve**

Based on various experimental studies, we describe auditory nerve activity by a population firing rate (black lines in Fig. 2), which is an average over several type-I AN fibers with similar characteristic frequencies. Being a population average, it comprises AN fibers with different spontaneous rates, thresholds, and dynamic ranges. We regard this as a reasonable approximation of the input of a downstream neuron that has synaptic contacts to many different AN fibers. The population response threshold is set to 0 dB SPL, which corresponds to the threshold of the most sensitive fibers. Below threshold there is...
spontaneous activity of 50 Hz, corresponding to an average over AN fibers with low and high spontaneous rates. For supra-threshold stimuli, the average population discharge rate grows with the stimulus intensity and saturates at 250 Hz. The dynamic range (20–80% rise) of the population response is 40 dB (Sachs & Abbas, 1974; Dallos & Harris, 1978; Liberman, 1978; Wang et al., 1997).

**Damage to cochlear hair cells alters AN rate-intensity functions**

Sensorineural hearing loss changes the response properties of the AN. We distinguish between hearing loss caused by loss of IHCs, loss of OHCs, and SD.

IHCs provide the main input to AN fibers. Each IHC is innervated by 10–30 AN fibers, but each AN fiber contacts only one IHC (Ryugo, 1992). Loss of IHCs therefore deprives associated AN fibers of their input, whereas the response properties of AN fibers associated with the remaining healthy IHCs seem largely unaffected (Wang et al., 1997). The degree of IHC loss is proportional to the decrease of the amplitude of the AN’s compound action potential, i.e. the summed discharge of all AN fibers (Wang et al., 1997). We therefore model IHC loss by scaling down the rate-intensity function of the AN fiber population in proportion to the amount of IHC loss. This simplification of the effects of IHC loss implies that spontaneous as well as maximum rates of the population response are reduced, but the response threshold remains unchanged (Fig. 2a and Materials and methods before Eqn 5).

OHCs are thought to act as active amplifiers inside the cochlea (reviewed in Geisler, 1998). Pure loss of OHCs, for example induced by ototoxic agents, typically increases the threshold of AN fibers, while spontaneous and maximum discharge rate remain mostly unaffected (Dallos & Harris, 1978; Schmiedt & Zwislocki, 1980). We therefore model OHC loss by an increase in the response threshold of the fiber population, where the increase is proportional to the amount of OHC loss. Based on experimental studies, the loss of all OHCs is assumed to elevate the threshold by 60 dB. Moreover, OHC loss steepens the rate-intensity function of the AN fiber population and reduces its dynamic range (Fig. 2b and Materials and methods before Eqn 6).

Stereocilia couple inner and outer hair cells to the tectorial membrane. They are damaged by noise overexposure (see, e.g. Wang et al., 2002b), which can also cause a loss of hair cells. SD elevates the response threshold (Liberman, 1984; Heinz & Young, 2004) and decreases the spontaneous firing rate of AN fibers (Liberman & Dodd, 1984), but SD does not change the maximum discharge rate (Liberman & Kiang, 1984). We therefore model SD caused by noise overexposure by an increase of the response threshold and a decrease in the spontaneous firing rate of the rate-intensity function of the AN fiber population. Changes are assumed to be proportional to the degree of SD. From the experimental literature, we estimate that the threshold is elevated by 80 dB for severe loss of stereocilia (100% SD), and that the spontaneous rate is reduced by a factor of two-thirds (Fig. 2c and Materials and methods before Eqn 7). Similar to pure OHC loss, we assume a steepening of the rate-intensity functions also for SD, which might not always be the case (Heinz & Young, 2004; see Discussion). Our description of the effects of SD comprises damage to or loss of the stereocilia of IHCs and OHCs, and it also includes the effects of the loss of OHCs, because we assume that the total loss of an OHC’s stereocilia has the same effect as the complete loss of an OHC.

In summary, each type of damage to the cochlea characteristically alters the rate-intensity function of the AN, which may trigger further changes along the auditory pathway.

**Sensorineural hearing loss changes the distribution of AN firing rates**

Before we can investigate the effects of homeostatic plasticity in downstream auditory neurons in response to sensorineural hearing loss, we first have to establish how the distribution of AN population firing rates is altered by cochlear damage. The fraction of time the AN population fires at some specific rate is determined by its rate-intensity function in conjunction with the distribution of sound intensities in an animal’s environment. Let us assume that the sound intensity levels of acoustic stimuli obey a Gaussian distribution with 40 dB mean and 25 dB standard deviation, so that most of the intensities are within the dynamic range of AN responses (Fig. 3a, see also Materials and methods). We note that the Gaussian distribution of sound levels corresponds to a long-tailed distribution of the linear amplitudes of acoustic stimuli, as found for natural sounds (e.g. Escabi et al., 2003). Moreover, we assume that AN rate-intensity functions are tuned to the distribution of sound intensities so that the firing rates of the AN have maximum information on the sound intensity (informax principle, Laughlin, 1981). This assumption is made in order to simplify further arguments and to allow an analytical approach (see Materials and methods). However, the detailed choice of the forms of both the rate-intensity function and the distribution of sound intensities are not critical for the main conclusions that can be drawn from our model; all unimodal distributions where the majority of sound intensity levels is within the dynamic range of the AN fibers yield similar results.

The probability density function of AN population rates for a healthy cochlea is shown in Fig. 3b (right panel). The probability of spontaneous AN activity is given by the fraction of time the sound intensity is below the response threshold of 0 dB. Therefore, the spontaneous firing rate of 50 Hz occurs with probability 0.05 (Fig. 3b, right panel, horizontal peak). For supra-threshold intensities, the probability density for firing at a given rate is constant in the interval between 50 and 250 Hz, due to our informax tuning assumption. In the following, we are going to evaluate three examples of cochlear damage: 30% IHC loss, 66% OHC loss, and 50% SD. The amounts of damage were chosen for similar threshold elevation (OHC loss and SD), similar reduction of the mean AN rate (IHC and OHC loss), and similar reduction of the spontaneous AN firing rate (IHC loss and SD).

The effect of 30% IHC loss is illustrated in Fig. 3c. As IHC loss was assumed to scale down the whole AN population response, the range of firing rates is reduced and the mean firing rate is decreased in proportion to the amount of IHC loss. Furthermore, the spontaneous firing rate is lowered, but the probability of spontaneous activity is unchanged compared to the healthy case. The result of 66% OHC loss is shown in Fig. 3d. OHC loss elevates the response threshold of AN fibers, while the spontaneous and the maximum firing rate remain unchanged. As an elevated threshold renders more stimuli subthreshold, the probability of spontaneous activity is increased from 0.05 to 0.5, which simply means that epochs of spontaneous firing occur more often. Consequently, driven activity occurs less frequently, and this is why OHC loss decreases the mean firing rate of the AN. Finally, an example for 50% SD is given in Fig. 3e. The response threshold is elevated by SD, and therefore the probability of spontaneous activity is increased, similar to OHC loss. However, SD also decreases the spontaneous firing rate of the AN, while the maximum firing rate remains constant. Thus, epochs of spontaneous firing occur more often, but the firing rate within such an epoch is decreased. As a consequence, the mean AN population firing rate is decreased more strongly than for the same threshold shift caused by OHC loss.
To summarize, the loss of IHCs, loss of OHCs, and SD all decrease the mean population firing rate of the AN. This is achieved, however, in different ways. Most relevant for a development of hyperactivity in our model is that OHC loss and SD mainly increase the probability of spontaneous firing, whereas a loss of IHCs scales down the AN population response.

**Homeostatic plasticity after hearing loss can lead to hyperactivity**

Let us now evaluate how the responses of a model neuron are changed through hearing loss. The model neuron could represent a downstream auditory neuron in the CN that receives excitatory input from the AN. We assume that the model neuron is innervated by AN fibers with similar characteristic frequencies that are described by the mean population firing rate. The neuron is modelled as a firing rate unit with a nonlinear response function \( R \) that includes a gain factor \( g \), which determines the impact of AN input on the model neuron’s firing rates.

The firing rate \( r \) of a model neuron in response to AN input at rate \( f \) is then given by \( r = R(f) = r_{\text{high}} \tanh (g \cdot f/r_{\text{high}}) \), with \( r_{\text{high}} \) being the maximum firing rate of the model neuron (see also Fig. 4a and b, and Materials and methods, Eqsns 10–12).

We propose that a CN neuron has some target mean firing rate \( r^* \) (when averaged over days) that is stabilized by homeostatic plasticity. In the model, this rate stabilization is implemented through an adjustment of the gain factor \( g \). This adjustment is in accordance with homeostasis through synaptic scaling (Turrigiano et al., 1998; Kilman et al., 2002) and neuronal excitability changes (Desai et al., 1999). Here, we do not model the dynamics of homeostatic plasticity, i.e. the time-course of \( g \), but simply focus on the equilibrium state that is reached as a result of homeostasis. Let us now illustrate the consequences of a homeostatic stabilization of the model neuron’s mean firing rate for the three examples of cochlear damage that we have introduced in Fig. 3.

IHC loss (30% in Fig. 4c) was argued to decrease mean, spontaneous and maximum firing rate of the AN, which, initially, also decreases the firing rate in the model neuron (Fig. 4c, panel \( g = 1 \)). In order to counteract this decrease, homeostatic plasticity increases the model neuron’s gain factor from \( g = 1 \) to some value \( g > 1 \). This restores the neuron’s mean firing rate to its reference value \( r^* \). Moreover, the neuron’s reconstituted response distribution (Fig. 4c, panel \( g = 1.43 \)) matches the one for 0% IHC loss (Fig. 4b, panel \( g = 1 \)). Thus, moderate loss of IHCs can be fully compensated by homeostasis in the framework of our model.

OHC loss (66% in Fig. 4d), on the other hand, was argued to increase the probability of spontaneous activity in both the AN and the model neuron without changing the spontaneous firing rate. When homeostatic plasticity increases the gain factor \( g \) to counteract the decreased mean firing rate, the distribution of the model neuron’s responses is drastically altered as compared to the healthy case. The maximum firing rate in the model neuron is elevated and, most importantly, also the spontaneous firing rate is increased (Fig. 4d, panel \( g = 1.54 \), see also Fig. 1).

SD (50% in Fig. 4e) was argued to increase the probability of spontaneous activity and to decrease the spontaneous rate in both the AN and the model neuron. Similar to OHC loss, homeostatic plasticity may recover the mean rate in the model neuron, but then the spontaneous rate is elevated as well (Fig. 4e, panel \( g = 1.89 \)).

Thus, homeostatic compensation of OHC loss, for example after administration of ototoxic drugs, or SD as induced by noise overexposure can lead to increased spontaneous firing rates or hyperactivity of auditory neurons downstream of the AN.

**Saturation of homeostasis decreases hyperactivity**

In Figs 2 and 3 we have indicated that severe cochlear damage leads to low AN activity. If this is to be compensated by homeostasis in the

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**Fig. 3.** Firing statistics of the AN model. (a) The distribution of sound intensity levels in units of dB is assumed to be Gaussian (40 dB mean, 25 dB standard deviation). (b–e, left panels) Rate-intensity functions of the AN population firing rate (b, healthy cochlea; c, 30% IHC loss; d, 66% OHC loss; and e, 50% SD). (Right panels) Firing-rate probability distributions of AN responses corresponding to the rate-intensity functions on the left and for the distribution of sound intensities in (a). Probability densities are on the ordinate, firing rates on the ordinate. The numbers at the horizontal ‘delta’ peaks of the distributions, e.g. 0.05 and 0.5, indicate the probability of occurrence of spontaneous activity for subthreshold stimuli. Shaded areas depict the distributions of firing-rate responses to super-threshold stimuli. Arrowheads denote mean firing rates. (b) Healthy cochlea (0% damage). Spontaneous activity is rare (probability 0.05). The range of firing rates is between 50 and 250 Hz. The mean activity is 145 Hz (arrowhead). (c) IHC loss (example 30%, dark grey) reduces spontaneous, mean (101 Hz) and maximum firing rates, while the probability of spontaneous activity remains at 0.05. (d) 66% OHC loss (medium grey) increases the AN response threshold by 40 dB without affecting the range of firing rates. Due to the threshold increase, the probability of spontaneous activity is increased to 0.5, and the mean firing rate is decreased to 100 Hz. (e) 50% stereocilia damage (light grey) increases the AN response threshold by 40 dB and decreases the AN’s spontaneous (33 Hz) and mean firing rate (88 Hz). The probability of spontaneous activity is increased to 0.5.
model neuron, large increases in response gain $g$ would be needed. However, in a biological system, physiological constraints are likely to impose an upper limit on homeostatic scaling. We therefore explore the influence of an upper limit on the gain factor $g$, which is estimated to be $g_{\text{max}} = 3$ (based on results in Turrigiano et al., 1998). If this saturation limit is reached, homeostatic plasticity is not able to restore the mean firing rate of the model neuron.

Figure 5 summarizes the effect of homeostasis and its saturation on the model neuron’s activity for all degrees (0–100%) of hair cell loss or stereocilia damage. For IHC loss (Fig. 5a), homeostasis saturates at 67% loss. Below this limit, the spontaneous firing rate is restored to its normal value after homeostasis. Degrees of damage beyond the saturation limit lead to spontaneous firing rates of the model neuron that are even lower than normal. On the other hand, if AN activity is decreased by OHC loss (Fig. 5b), the saturation limit of homeostasis is never reached, at least not for the set of parameter values we found feasible to describe OHC loss. The neuron’s spontaneous firing rate after homeostasis is thus a monotonically increasing function of the degree of OHC loss. Finally, SD can lead to saturation of homeostasis in the model neuron (Fig. 5c). Below the saturation limit of 67% SD, the neuron’s spontaneous firing rate increases with increasing SD. If SD is larger than the saturation limit, the spontaneous firing rate decreases again. The maximum, or kink, of the neuron’s spontaneous rate occurs at the saturation limit of homeostasis.

**Non-AN input boosts the development of hyperactivity**

Homeostatic plasticity is a mechanism that can scale all synapses of a neuron (Turrigiano, 1999). Therefore, a homeostatic increase in response gain to compensate for decreased AN activity could also influence non-auditory inputs. The CN receives input from a variety of other brain regions in addition to feedforward input from the AN. The most diverse set of such additional inputs is found in the DCN. There are projections from the contralateral CN (Cant & Gaston, 1982; Shore et al., 1992), top-down connections from the cortex (Weedman & Ryugo, 1996; Jacomme et al., 2003), and inputs from the somatosensory system (Kanold & Young, 2001; Zhou & Shore, 2004).

To evaluate the consequences of non-auditory input to the model neuron, we simply consider a constant excitatory input $f_{\text{add}}$ in addition to the variable input $f$ from the AN (Fig. 6a). Both inputs are scaled by the gain factor $g$ so that the model neuron’s rate reads $r = R(f + f_{\text{add}}) = r_{\text{high}} \tanh(g(f + f_{\text{add}} - \theta)/r_{\text{high}})$, where we have introduced a response threshold $\theta$. We set this threshold to $\theta = f_{\text{add}}$. 

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**Fig. 4.** Model for a downstream auditory neuron in the cochlear nucleus (CN) and illustration of the result of homeostatic plasticity. (a) The model neuron receives excitatory input at rate $f$ from a population of AN fibers. The model neuron’s output firing rate $r = R(f) = r_{\text{high}} \tanh(g \cdot f/r_{\text{high}})$ is determined by the response function $R$ with its adjustable gain factor $g$ and constant maximum firing rate $r_{\text{high}} = 300$ Hz. Homeostatic plasticity adjusts the mean of the output rate $r$ by changing the gain factor $g$. (b) Healthy cochlea (no damage). The probability of AN fibers to fire at a given rate (top; identical to Fig. 3B) is mapped by the response function (bottom left) to the firing probability of the model neuron (right panel). The neuron’s mean firing rate is 130 Hz (arrowhead), the spontaneous firing rate is 50 Hz, and the maximum firing rate is 205 Hz (horizontal dotted lines). The probability 0.05 of spontaneous firing in the model neuron is the same as in the AN. All probability distributions are at identical scales. (c–e) Same as in (b), but for different types of damage to the cochlea (grey), both before ($g = 1$) and after homeostasis ($g > 1$). (c) 30% IHC loss (dark grey) decreases the mean firing rate of the model neuron to 96 Hz and the spontaneous firing rate to 35 Hz (panel $g = 1$). Homeostatic plasticity increases the gain to $g = 1.43$ (dashed line in bottom left panel), which fully restores the neuron’s response distribution (see b). (d) 66% OHC loss (medium grey) increases the probability of spontaneous activity to 0.5 without affecting the range of firing rates. The mean firing rate of the model neuron is decreased to 92 Hz (panel $g = 1$). Homeostasis increases the gain to $g = 1.54$ (dashed line in bottom left panel), but this substantially alters the neuron’s response distribution (panel $g = 1.54$). Especially, the spontaneous firing rate is increased from 50 to 76 Hz. (e) 50% SD (light grey) decreases the mean firing rate in the model neuron to 80 Hz and the spontaneous firing rate to 33 Hz (panel $g = 1$). After homeostasis (panel $g = 1.89$), the spontaneous firing rate is increased to 62 Hz. 

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*European Journal of Neuroscience, 23*, 3124–3138
so that the previous scenario without additional input in Figs 3–5 can be directly compared to the scenario with additional input in Fig. 6. For the healthy case with $g = 1$, both scenarios are identical (Fig. 6b). For homeostatic scaling that leads to $g > 1$ however, additional excitatory input to the model neuron gives rise to marked differences that depend on the type of cochlear damage.

We found that IHC loss can also lead to hyperactivity if there is additional excitatory input to the model neuron (Fig. 6c). The higher the firing rate of the additional input the more hyperactivity. Moreover, the saturation point of homeostasis is shifted towards greater damage. The situation is different for OHC loss; the results obtained with additional input are very similar to those obtained without (Fig. 6d).

For SD, the model with additional input exhibits higher spontaneous firing rates after homeostasis than the model without. Also, the saturation point of homeostasis is shifted towards greater damage (Fig. 6e).

In conclusion, when the activity of the AN, which provides excitatory input to the CN, is reduced because of cochlear damage, homeostatic plasticity increases the effective response gain that affects all inputs. Therefore, additional non-auditory inputs are also amplified and then contribute to hyperactivity. This mechanism suggests how, for example, somatosensory input could be involved in the generation of tinnitus.

**Model results for cochlear pathologies associated with tinnitus**

In humans, acoustic trauma and treatment with cisplatin (used in cancer therapy) are often associated with tinnitus. Animal studies demonstrate that both acoustic trauma and cisplatin administration damage cochlear hair cells and lead to hyperactivity of DCN neurons (Kaltenbach et al., 1998, 2000; Brozoski et al., 2002; Kaltenbach et al., 2002, 2004). We are now going to present results of our model for the corresponding characteristic patterns of cochlear damage, where combinations of OHC and IHC loss, or SD and IHC loss, concurrently influence the AN population response (see Materials and methods, Eqns 8 and 9). We therefore consider a tonotopic array of CN neurons receiving input from the corresponding tonotopic loci of the cochlea via the AN (Fig. 7a).

Systemic cisplatin administration can cause severe OHC loss in the basal segment of the cochlea that responds to high frequencies, whereas IHCs are typically only affected to a limited degree (Kaltenbach et al., 2002; van Ruijven et al., 2004). Additionally, cisplatin can lead to a demyelination of AN fibers innervating the basal turn of the cochlea (van Ruijven et al., 2004, 2005). Therefore, in our framework we approximate the effects of cisplatin-induced combined damage to IHCs and AN fibers by moderate IHC loss. As for the spatial pattern of cochlear damage, we consider severe OHC loss.

**Fig. 5. AN activity, gain factor, and CN activity after homeostasis in dependence upon the degree of IHC loss, OHC loss, and SD. (a1–a3) IHC loss. (a1) AN firing rates. Spontaneous (solid line), mean (dashed line), and maximum (dotted line) firing rate are reduced in proportion to the amount of IHC loss. The shaded area illustrates the range of firing rates. (a2) Gain factor after homeostasis. Homeostatic scaling saturates because we have imposed an upper bound on the gain factor (here: $g_{\text{max}} = 3$). (a3) CN model neuron firing rates after homeostasis. The mean firing rate (dashed line) is restored to its healthy value for up to 67% IHC loss. Beyond this limit, when homeostasis is saturated, the neuron’s rates decrease with increasing loss of IHCs. (b1–b3) OHC loss. (b1) The mean activity of the AN decreases with increasing OHC loss, but the range of firing rates, from spontaneous to maximum rate, remains constant. (b2) The gain factor after homeostasis increases with increasing OHC loss. (b3) The mean firing rate in the model neuron is restored to its target value for up to 67% SD, and the spontaneous activity is increased. For larger amounts of SD, the mean and spontaneous rate decline; the maximum rate stays constant.

(c1–c3) Stereocilia damage (SD). (c1) Mean and spontaneous AN firing rates are decreased by SD. (c2) The gain factor saturates for more than 67% SD. (c3) The mean firing rate in the model neuron is restored to its target value for up to 67% SD, and the spontaneous activity is increased. For larger amounts of SD, the mean and spontaneous rate decline; the maximum rate stays constant.

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In conclusion, when the activity of the AN, which provides excitatory input to the CN, is reduced because of cochlear damage, homeostatic plasticity increases the effective response gain that affects all inputs. Therefore, additional non-auditory inputs are also amplified and then contribute to hyperactivity. This mechanism suggests how, for example, somatosensory input could be involved in the generation of tinnitus.
For SD, the maximum increase in spontaneous firing rate depends on the additional input in Fig. 4B. Spontaneous firing rate of the model neuron after IHC loss and homeostasis for different values of additional input. Without additional input, the spontaneous firing rate is only elevated at a single peak that is associated with the edge of the stereocilia lesion (Fig. 7e, upper panel, \( f_{\text{add}} = 0 \) Hz). The peak structure is caused by the saturation of homeostasis (compare Fig. 5c). At frequencies where IHCs are lost in addition to severe SD, spontaneous firing rates can be even lower than before. With increasing additional input (25 and 50 Hz in Fig. 7e, upper panel), the peak in the spontaneous firing rate profile is shifted towards higher frequencies because homeostasis saturates at greater damage. Moreover, the peak becomes broader for 25 Hz additional input to finally extend over large parts of the tonotopic array for 50 Hz, at which the spontaneous firing rate is strongly elevated for all neurons that receive input from the damaged regions of the cochlea. The latter hyperactivity profile for 50 Hz additional input is similar to those observed experimentally in the DCN after severe unilateral acoustic trauma (Kaltenbach et al., 1998, 2000, 2004).

Hyperactivity caused by unilateral acoustic trauma was shown to persist even after cochlear ablation (Zacharek et al., 2002). Spontaneous firing rates were decreased by the ablation, but remained increased compared to the healthy case. To capture this experiment in the model, we first let homeostasis increase the model neuron’s gain to compensate for the effects of acoustic trauma. Then we remove all AN activity, leaving only the additional input (50 Hz in our example). As homeostasis is a slow process, the gain remains adjusted to acoustic trauma for at least several hours after the ablation. The additional input is thus amplified, leading to spontaneous firing rates in the model that are reduced compared to the situation before the ablation (Fig. 7e, lower panel, ‘ablated’), but still elevated, and the distribution of spontaneous rates reflects the pattern of cochlear damage. After longer waiting times on the order of days, homeostatic plasticity adapts the neuron’s gain to the only remaining input \( f_{\text{add}} \). In the model, \( f_{\text{add}} \) is constant across frequencies, leading to a flat profile of elevated spontaneous firing rates (dotted line in Fig. 7e, lower panel) when homeostasis is saturated at its upper bound. In experiments, the equilibrium distribution of spontaneous firing rates after AN section will depend on the distribution and activity of additional inputs across frequency channels in the auditory system.

Reversing hyperactivity through additional acoustic stimulation

Having established how hyperactivity and possibly tinnitus could develop through homeostatic plasticity after hearing loss, we are now able to evaluate how the pathologic changes could be reversed through additional sensory stimulation. It is obvious that hyperactivity could
be reversed in our model by restoring the regular distribution of AN firing rates, which corresponds to a perfect 'hearing aid'. A simpler and feasible way, however, would be permanent additional stimulation through specially adjusted noise devices. Let us now discuss the effects of different stimulation strategies on hyperactivity in our model. We evaluate a white-noise stimulus, as often used in tinnitus therapy (Hazell, 1999), and a specially designed matched-noise stimulus for an example of noise-induced hearing loss with severe stereocilia damage that strongly elevates hearing thresholds in the high-frequency range (Fig. 8a, upper panel). We employ the model variant without additional input, as it exhibits a distinct peak in the spontaneous firing-rate profile after homeostatic plasticity, which could be interpreted as the basis for a tone-like tinnitus sensation (Fig. 8a, lower panel). The peak is caused by the saturation of homeostasis (see also Figs 6e and 7e).

We first explore white-noise stimulation at 40 dB (Fig. 8b). Above ∼3 kHz it is below the hearing threshold. The mean AN firing rate is increased by the additional stimulation only in the low-frequency range (not shown), where homeostatic plasticity then decreases the gain in the model neurons to compensate for the increased AN input (Fig. 8b, middle panel). Neurons in the high-frequency range are not affected, and the hyperactivity peak is unchanged. During stimulation, the white-noise stimulus evokes firing rates in the model neurons that are higher than those at the hyperactivity peak, possibly masking the

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**Fig. 7.** Two examples of model results for cochlear pathologies that can lead to tinnitus in humans. (a) Illustration of the tonotopic connection between cochlea and CN. (b) Cochleograms indicate damage induced by systemic cisplatin administration. OHC loss extends over large parts of the cochlea (top panel). Additional damage to IHCs and AN fibers is approximated in our model by moderate IHC loss (bottom panel). (c) Spontaneous activity of CN model neurons after homeostasis as a function of a neuron’s location along the tonotopic axis for three different rates (0, 25, and 50 Hz) of the additional input. Hyperactivity is observed in those model neurons that receive input from regions of the cochlea where OHCs are lost. Without additional input, extra IHC loss leads to lower spontaneous firing rates than the same amount of OHC loss alone. (d) Cochlear damage through noise-induced hearing loss. Stereocilia are severely damaged over large parts of the cochlea (top panel). IHC loss is less pronounced (bottom panel). (e) CN spontaneous rate after homeostasis. (Top panel) The amount and extent of hyperactivity heavily depends on the strength of the additional input, ranging from a single peak associated with the edge of the cochlear lesion for $f_{add} = 0$ Hz to strongly elevated spontaneous firing rates over large parts of the tonotopic axis for $f_{add} = 50$ Hz. Peak-like structures are caused by the saturation of homeostasis. (Bottom panel) For strong additional input (here 50 Hz), hyperactivity can persist after cochlear ablation. Immediately after the ablation, the profile still reflects cochlear damage (lower solid line), but later turns into a flat profile for the chronic case (dotted line).
tone-like tinnitus (Fig. 8b, lower panel, dashed line). Immediately after the white-noise stimulus is turned off, however, the hyperactivity peak is even more pronounced (Fig. 8b, lower panel, thick grey line) than before the additional stimulation (see Fig. 8b), as the homeostatic adaptation has lowered the gain in the low-frequency range and thus has decreased the spontaneous firing rates there. An unspecific white-noise stimulus therefore masks a hyperactivity peak in the model, but even exaggerates it after the stimulus is turned off.

In a second scenario, we derive a matched-noise stimulus (see Materials and methods) that reverses hyperactivity and leads to a flat profile of the spontaneous firing rate across the tonotopic axis of the model neurons after homeostasis, as in the healthy situation (Fig. 8c, upper panel). This stimulus is 1.5–4 dB above the hearing threshold only in the high-frequency range, where hearing is impaired, and therefore increases the mean firing rate of AN fibers in this frequency range. As a consequence, homeostatic plasticity is triggered in those model neurons receiving input from the additionally stimulated AN fibers, where it lowers the pathologically increased gain factors. After homeostasis, the matched-noise stimulus evokes low to medium firing rates in the model (Fig. 8c, lower panel, dashed line), thus homeostasis does not suppress the response to the stimulus. Once stimulation is turned off, the spontaneous firing rate profile across the tonotopic axis is flat (Fig. 8c, lower panel, thick grey line). Hyperactivity would only slowly reemerge after prolonged periods without stimulation, and the time-course of reemergence is governed by the time-scale of days of homeostatic plasticity. It may therefore be possible to find a stimulation paradigm where intervals with and without stimulation are interleaved, which provides an efficient suppression of hyperactivity without the necessity of constant stimulation.

The observation that in our model additional acoustic stimulation can reverse hyperactivity is matched by the findings that hearing aids (Surr et al., 1999), noise devices (Schneider et al., 1999), and cochlear implants (Ito & Sakakihara, 1994; Quaranta et al., 2004) can reduce perceived tinnitus severity. Our matched-noise stimulus, however, is different from common masking approaches with unspecific broadband stimuli as it is designed not solely to mask tinnitus, but to decrease elevated spontaneous activity that constitutes the basis for the tinnitus sensation.

Discussion

We have presented a phenomenological model of the early auditory pathway to assess the question of how sensorineural hearing loss could lead to pathologically increased spontaneous firing rates (hyperactivity) in the auditory brainstem, which may be perceived as tinnitus. There are, to our knowledge, no other models on the development of tinnitus-related hyperactivity through homeostatic plasticity. Our model is based on a simplified description of the firing-rate response of AN fibers to acoustic stimuli, the effects of hearing loss through damage to cochlear hair cells, the responses of downstream auditory
neurons in the CN to input from the AN and other sources, and the effect of a homeostatic plasticity mechanism that stabilizes the mean firing rate of CN neurons at a constant level.

In the healthy auditory system, homeostatic plasticity could help to ensure that auditory neurons are active within the right range of firing rates independent of the prevailing acoustic environment. Homeostatic plasticity in auditory neurons might also prevent us from perceiving spontaneous neuronal activity as sound. For pathologically altered processing in the cochlea, however, this plasticity mechanism could also have detrimental effects. We propose that homeostatic plasticity can lead to hyperactivity in cochlear nucleus neurons when the ratio between the spontaneous and the mean firing rate in the AN is decreased. As sensorineural hearing loss always lowers the mean firing rate in the AN, the relative change of the spontaneous rate is crucial. We found that in a generic model of IHC loss that preserves the ratio of mean and spontaneous activity in the AN, restoring of the activity statistics of second-order neurons is possible. Because both OHC loss and SD decrease the ratio between the mean and the spontaneous firing rate of the AN, homeostatic scaling leads to elevated spontaneous firing rates. Constant additional (non-auditory) input to a cochlear nucleus neuron can boost the development of hyperactivity because this input is also amplified after hearing loss, as homeostasis is a global mechanism affecting all synapses that provide input to the neuron.

The model is in agreement with several animal studies demonstrating that acoustic trauma can lead to increased spontaneous firing rates in the DCN (Brozoski et al., 2002; Kaltenbach et al., 2004) and to behavioral signs of tinnitus (Brozoski et al., 2002; Heffner & Harrington, 2002; Kaltenbach et al., 2004). Interestingly, the strength of the behavioral evidence for tinnitus is correlated to the amount of hyperactivity in the DCN (Kaltenbach et al., 2004). The DCN, however, need not be the sole generator of tinnitus-related activity in the auditory system, as DCN ablation does not seem to abolish behavioral signs of tinnitus (Brozoski & Bauer, 2005). If the proposed mechanism of activity stabilization is relevant for various types of neurons along a sensory pathway, hyperactivity could arise at any stage that is confronted with decreased excitatory input. Ablation of the DCN, for example, removes excitatory input to subsequent stages such as the inferior colliculus. It is thus conceivable that homeostasis triggers hyperactivity there.

In our model, homeostatic plasticity restores the mean firing rate of a second-order auditory neuron after hearing loss. The fraction of time the neuron spends firing at its spontaneous rate, however, cannot be decreased by homeostasis or other plasticity mechanisms, because this fraction is fixed by the response threshold of AN fibers. This fact applies to all neurons along the auditory pathway. Therefore, even if homeostatic plasticity simultaneously occurs at several stages of the auditory system, pathological neuronal activity generated at one processing stage cannot be reverted to healthy activity distributions by homeostasis in subsequent stages. As spontaneous firing after hearing loss typically has a higher probability than before, its contribution to the mean activity is increased at all stages. Restoring the mean rate is therefore to be expected to increase the spontaneous rate throughout the auditory system.

Following sensory deprivation, indications of a homeostatic mechanism have indeed been seen at various stages of the auditory pathway. In the inferior colliculus of gerbils, for example, bilateral deafening leads to increased EPSC amplitudes and increased IPSC equilibrium potentials (Vale & Sanes, 2002), suggesting that the balance between excitation and inhibition is shifted in a homeostatic fashion. Moreover, in the cochlear nucleus of chinchillas, acoustic trauma temporarily increased glutamatergic synaptic transmission (Muly et al., 2004). Increased EPSC amplitudes were also observed in the anteroventral cochlear nucleus of congenitally deaf mice in response to electrical stimulation of the AN (Oleskevich & Walmsley, 2002). Furthermore, glycinergic inhibition in the DCN was persistently weakened following unilateral cochlear ablation (Suneja et al., 1998a, 1998b) or age-related hearing loss (Caspar et al., 2005). Finally, in the auditory cortex of gerbils, increased excitability as well as increased excitatory and decreased inhibitory synaptic transmission were measured after bilateral cochlear ablation (Kotak et al., 2005). Homeostatic plasticity may thus be involved in activity-dependent regulatory processes throughout the auditory system.

Further evidence for homeostasis-like mechanisms in the auditory pathway comes from the observed time scale of changes after sensory deprivation. Hyperactivity in the DCN develops within days after hearing loss. Although cochlear damage and thus the auditory threshold shift is already present two days after acoustic trauma, no increase in DCN spontaneous firing rates is observed at that time (Kaltenbach et al., 1998). Five days after acoustic trauma, however, hyperactivity is fully developed (Kaltenbach et al., 2000). This finding indicates that hyperactivity could be involved, as changes through homeostasis also occur on a time-scale of days (Turrigiano et al., 1998). Reminiscent of homeostatic plasticity, Formby et al. (2003) found a gain control mechanism that regulates loudness perception depending on the overall amount of sensory input to the human auditory system. The gain control operated, again, on a time-scale of days.

Homeostatic regulation of neuronal activity levels might be a general principle in sensory pathways. In the visual system of rats (postnatal day 15), hyperactivity of cortical neurons has been observed after two days of visual deprivation (Maffei et al., 2004): excitatory synaptic connections were strengthened, inhibitory synapses were weakened, and the spontaneous firing rates of specific cortical neurons were increased; restoring vision reversed the changes. In the somatosensory system, our findings might also be applicable to the phenomenon of phantom limb sensations that can arise after amputations. Another modelling study indicates that homeostatic plasticity after deafferentation could be involved in post-traumatic epileptogenesis (Houweling et al., 2005).

To demonstrate that homeostatic plasticity after hearing loss can lead to increased spontaneous firing rates in second-order neurons, we deliberately chose a phenomenological modelling approach that is based on several simplifying assumptions. In our model of the AN population rate, for example, the shape of the rate-intensity function is coupled to the shape of the intensity distribution by the infomax tuning assumption. This results in a steepening of rate-intensity functions for elevated thresholds, which matches observations for isolated OHC loss (Harrison, 1981). SD also elevates thresholds, but single AN fibers can display rate-intensity functions that are even shallower than normal (Heinz & Young, 2004). Shallower rate-intensity functions, however, would lead to a greater reduction of the mean AN rate. In our model, more homeostatic compensation would then be needed in second-order neurons, resulting in more hyperactivity. Thus, for the development of hyperactivity, steepening of the rate-intensity functions is the more conservative assumption. Another simplifying assumption in our model is that we consider only excitatory input, whereas neurons in the CN are part of an elaborate circuitry containing a variety of inhibitory interneurons (Rhode & Greenberg, 1992; Young & Davis, 2002). This is most evident, for example, in the responses of type IV neurons of the DCN, which are characterized by inhibitory sidebands and nonmonotonic rate-intensity functions (Spirou & Young, 1991; Young & Davis, 2002). Because neurons in the cochlear nucleus are part of a sensory pathway, it is likely that even for such...
complex response properties the net effect of natural acoustic stimuli is excitatory, leading to a mean firing rate that is above the spontaneous one. It is unknown how the mean firing rate of these neurons changes as a result of hearing loss in behaving animals, and firing statistics of auditory neurons in natural environments are not available. However, we regard it as reasonable that cochlear damage decreases the mean activity level in a large fraction of neurons in the cochlear nucleus. Decreased mean activity could then trigger homeostatic plasticity, leading to increased spontaneous firing rates. This conclusion is independent of details of information processing in the auditory pathway.

The presented model is as simple as possible to exhibit the consequences of homeostatic plasticity in the auditory system. The model therefore has no free parameters, that is, parameters do not need to be fitted. Several extensions of the model are possible in order to test whether its features are robust with respect to more biophysical details. A more detailed model of the basilar membrane, hair cells and the auditory nerve could be used (Zhang et al., 2001; Sumner et al., 2003). The second-order neuron could be described through a conduction-based unit (Kanold & Manis, 2001), and inserted into a neuronal network with inhibition (Reed & Blum, 1995; Blum & Reed, 1998; Franosch et al., 2003). Finally, feedback through the efferent auditory system could be considered, and other damage and plasticity mechanism could be incorporated, like excitotoxicity and subsequent sprouting of new synapses, or long-term potentiation and depression at individual synapses. Also the time-course of homeostatic plasticity could be investigated. These extensions are, however, way beyond the scope of this article. Such extensions would lead to large amount of additional parameters that would add many degrees of freedom to the model, which need to be reasonably constrained to reach viable predictions. That is why we chose to utilize a minimal model that emphasizes the most important features of this complex system. Nevertheless, we hope that the presented model provides a basis for deriving more detailed models of tinnitus development.

Even though our model is extremely simple, the relation between the pattern of cochlear damage and the resulting profile of hyperactivity in a tonotopic array of model neurons matches observations in the DCN of animals (e.g. Kaltenbach et al., 2002). We note that for stereocilia damage resembling noise-induced hearing loss, the model generates activity peaks in neurons with best frequencies above the edge of the cochlear lesion. These peaks could be interpreted as a basis for tinnitus sensations with tonal characteristics and a pitch at a frequency where cochlear damage/hearing loss exceeds a certain degree. A similar association between tinnitus pitch (Henry et al., 1999) or tinnitus spectrum (Norena et al., 2002) and the extent of hearing loss has been observed in humans. It is still unclear, however, why some patients with hearing loss develop tinnitus whereas others do not. Moreover, not all tinnitus patients have impaired hearing, although there is evidence that tinnitus patients without obvious signs of hearing loss might have restricted cochlear damage that is not detected by conventional audiometry (Weisz et al., 2005). Our work indicates that the exact type and spatial pattern of cochlear damage as well as the strength of non-auditory inputs are crucial for the development of hyperactivity. In human subjects, however, information on the type and amount of cochlear damage can only be obtained indirectly and to a very limited extent, and little is known about the variability of non-auditory inputs to the auditory pathway.

The proposed model for the development of hyperactivity complements the so-called ‘Neurophysiological Model’, which assumes that a tinnitus percept is generated by abnormal neuronal activity in the auditory periphery that is amplified through attentional and emotional processes (Jastreboff, 1999). From the ‘Neurophysiological Model’, the Tinnitus Retraining Therapy has been derived (Jastreboff & Jastreboff, 1999), which uses a combination of psychological counseling with masking devices and hearing aids. Our model explains why hearing loss can induce increased spontaneous firing rates in the early auditory pathway that may constitute the basis of a tinnitus sensation, and it also provides a biologically plausible and consistent framework for understanding how tinnitus-related hyperactivity might be reduced through appropriate external stimulation. We hope that this understanding will lead to improved strategies for a treatment of tinnitus.

Acknowledgements

We would like to thank Manfred Gross, Andreas Herz, Ovidiu König, Paula Kuokkanen, Christian Leibold, and Martin Stemmler for most helpful discussions on this work. This research was supported by the Deutsche Forschungsgemeinschaft (Emmy Noether Programm: Ke 788/1–3, SFB 618 ‘Theoretical Biology’, TP B3) and the Bundesministerium für Bildung und Forschung (Bernstein Center for Computational Neuroscience Berlin, 01GQ0410).

Abbreviations

AN, auditory nerve; CF, characteristic frequency; CN, cochlear nucleus; DCN, dorsal cochlear nucleus; IHC, inner hair cell; OHC, outer hair cell; SD, stereocilia damage.

References


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