

# Structure and function of cochlear afferent innervation

Alexander C. Meyer and Tobias Moser

Department of Otorhinolaryngology, University of Göttingen, Göttingen, Germany

Correspondence to Dr Alexander C. Meyer, HNO-Klinik der Universitätsmedizin, 37099 Göttingen, Germany  
Tel: +49 551 39 22803; fax: +49 551 39 12950; e-mail: ameyer4@gwdg.de

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## Purpose of review

For the perception of sound, acoustic signals need to be encoded into a neuronal code. This takes place at the inner hair cells of the organ of Corti and the afferent fibers of the auditory nerve. We will review the current knowledge of the anatomy and function of these elements as well as their connection – formed by the afferent inner hair cell synapse.

## Recent findings

Depending on their tonotopic location, inner hair cells are innervated by 5–30 dendrites of spiral ganglion neurons. Electrophysiological recordings from single fibers demonstrate – apart from a high-frequency selectivity – a pronounced heterogeneity in their response to sound of varying intensity. The source as well as the function of this heterogeneity is not well understood but recent publications have suggested several mechanisms, including variations in the presynaptic  $\text{Ca}^{2+}$  influx and subsequent transmitter release, the postsynaptic sensitivity to neurotransmitter and electrical as well as anatomical variability of single fibers. These mechanisms might act together to expand the dynamic range of sound that can be encoded.

## Summary

Classical studies as well as recent publications demonstrate that sound encoding at the inner hair cell afferent synapse involves mechanisms leading to tonotopic frequency separation and distribution of intensity coding over many neuronal channels.

## Keywords

auditory nerve, inner hair cell, ribbon synapse, sound encoding, spiral ganglion neuron

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## Introduction

Encoding sound signals into a neuronal code is central in the process of hearing. However, it is not merely a simple sampling procedure in the inner ear. In order to enable the brain to perform such challenging tasks like sound localization or understanding of speech, the neuronal code must faithfully preserve signal properties such as intensity and timing.

Extracellular recordings from single fibers of the auditory nerve have been performed for more than half a century [1–4], providing us with a very detailed picture of how auditory information is encoded. The firing pattern in response to sound stimuli of spiral ganglion neurons (SGNs), which form the afferent part of the auditory nerve, exhibits a number of properties that are unique and most likely contain all relevant information needed for interpreting the signal. Probably the most prominent one is the frequency selectivity of the single fiber. Already early electrophysiological recordings from the auditory nerve [1,3] showed that single fibers preferentially increase their discharge frequency above spontaneous rate when acoustically stimulated at an individ-

ual, characteristic frequency. Mapping the response threshold over the entire audible spectrum displayed the tuning curve of that fiber. Typical tuning curves show a sharp minimum at the characteristic frequency and a rather high threshold at other frequencies [1,3,4]. Recordings from many fibers of the auditory nerve showed that their characteristic frequencies are widely distributed over the entire range of the audible spectrum.

Encoding of broad-spectrum sound signals into distinct channels of a narrow frequency band probably represents one of the earliest steps of processing in the auditory system. Starting with the mechanical cochlear frequency dispersion [5], the sharpness of frequency separation is further enhanced by outer hair cell amplification [6,7]. As a result, we find a fine-grained place code for sound frequency along the organ of Corti.

## Hearing threshold and innervation density

Perception of sound, however, is not equal at different tonotopic locations. This immediately becomes evident when looking at hearing thresholds. Frequency-dependent hearing thresholds have been determined in many

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species including cat [3], guinea pig [8], chinchilla [7], Mongolian gerbil [9,10] and mouse [11], either by behavioural testing [12], evoked response audiometry [13], auditory steady-state responses [14], electrocochleography (compound action potential) or single unit recordings from the auditory nerve [9]. Although the range of audible frequencies varies, all species typically show a region where hearing thresholds are lowest in their mid-frequencies. At the lower or higher end of the spectrum, thresholds usually increase by 20 dB SPL or more. There is no doubt that the signal transfer function of the entire hearing apparatus largely reflects the acoustic properties and the micromechanics of the outer and middle ear [5,15]. However, it is becoming clear lately that this might be just half the truth. From a number of recent publications, we learn that also the sensory elements of the cochlea – inner hair cells (IHCs) as well as the afferent nerve fibers – are tuned differently depending on their tonotopic location.

First reports on tonotopic variations in the cochlea date back some 30 years, when the anatomy of the organ of Corti and its afferent innervation was studied with electron microscopy. In cat, Spoendlin [16] reported a maximum in the innervation density in the mid-cochlear regions, a finding that was later confirmed in other species [17,18]. However, results from these studies were in part limited by the fact that data from electron microscopy, although excellent in resolution, typically comprise low sample sizes due to the high effort required. But already from these data, Ehret and Frankenreiter [19] suggested that the highest innervation density might coincide – for functional reasons – with the region of best hearing.

A different approach to the tonotopy of innervation density has been undertaken by Meyer *et al.* [20\*\*] using light microscopy. They labelled presynaptic ribbons, the morphological hallmark of the afferent, ribbon-type IHC synapse, in mice and gerbil with immunofluorescent dyes [21]. Synapses could then be counted over the entire length of the cochlea. Previous studies had shown that in mammals, each SGN sends out one unbranched, myelinated dendrite to contact a single IHC, which, in turn, forms synapses with a variable number (previous reports between 5 and 30) of SGN dendrites [22–24]. Therefore, a map of afferent synapses should also closely resemble the density of auditory fibers. As a result, in both species, a mid-cochlear region was identified which showed a maximum of 17 and 23 synapses per IHC in mouse and gerbil, respectively. This is more than double the number of synapses, an IHC at the far apical or basal region holds in these animals. So far, there are only few data on tonotopical variations in the function of the IHC synapse itself. For gerbil, Johnson *et al.* [25] reported a higher calcium efficacy of release and higher refilling rate in IHC at the more basal end of the cochlea. However,

experiments in mice demonstrated that transmitter release essentially scales with the number of synapses in hair cells of different tonotopic locations, suggesting a rather uniform function [20\*\*]. These seemingly contrasting findings may reflect different properties of the ‘high-frequency cochlea’ of the mouse (4–100 kHz [11]) and the ‘lower frequency cochlea’ of the gerbil (0.3–30 kHz [9]).

### Anatomical and functional basis of single-unit firing patterns

In gerbil as well as mouse, place-frequency maps of the cochlea have been established based on single unit recordings and subsequent anatomical reconstructions [9,11]. From these data, regions with the highest innervation density correspond to frequencies at which sound perception, determined from hearing thresholds either by evoked response audiometry or electrocochleography, is most sensitive. This raises the interesting question of cause or coincidence – in other words, is a large number of auditory fibers necessary to ensure high sensitivity of sound perception? For one, it is important to note that much of the dependence of acoustic sensitivity on sound frequency originates from the ear’s passive and active micromechanics upstream of sound coding, as is evident from recordings of otoacoustic emissions. For two, auditory threshold is quite robust against changes in afferent synapse or fiber number [26\*,27\*]. However, other properties and readouts of auditory systems function are likely dependent on the number of independent information channels to the brain. Analyzing the properties of single fiber responses to sound stimulation suggests why sampling information from an IHC by many fibers may be advantageous:

A finding from numerous single-unit recordings [1,4,10] was, that fibers even with identical characteristic frequency, potentially originating from the same or neighbouring IHCs, vastly diverge in their spiking behaviour. Spontaneous spiking rates in the absence of sound stimulation range from near zero to more than 100 spikes/s [3]. Remarkably, the spiking rate of a fiber positively correlates with its sensitivity to sound. High spiking rate fibers increase their spiking rate already at low sound pressure, but at larger intensity, their rate saturates early [1,28]. In contrast, low spiking rate fibers activate at higher sound intensities and in general show a much shallower rate of rise with late or no saturation. It has been suggested that the purpose of this mechanism is to increase the dynamic range of intensity coding. An ensemble of fibers originating from a single IHC would be able to encode very soft sounds with high sensitivity and at the same time have the ability to transmit intensity increments at higher volumes by recruiting more fibers. Thus, for the cochlear region of best hearing, where the hearing threshold is

lowest and, therefore, the dynamic range to be encoded is largest, a higher number of fibers would be favourable. We note here that this combinatory approach may not be the only mechanism to cope with wide dynamic range encoding. In addition, the adaptation of SGN spike rate likely contributes to fulfilling this challenging task (dynamic range adaptation [29,30]).

Although the diversity of auditory fibers is known already for long, the mechanisms behind it, however, are not well understood. A number of studies, including very recent ones, have suggested possible origins for functional fiber heterogeneity, which we discuss here (summarized in Fig. 1).

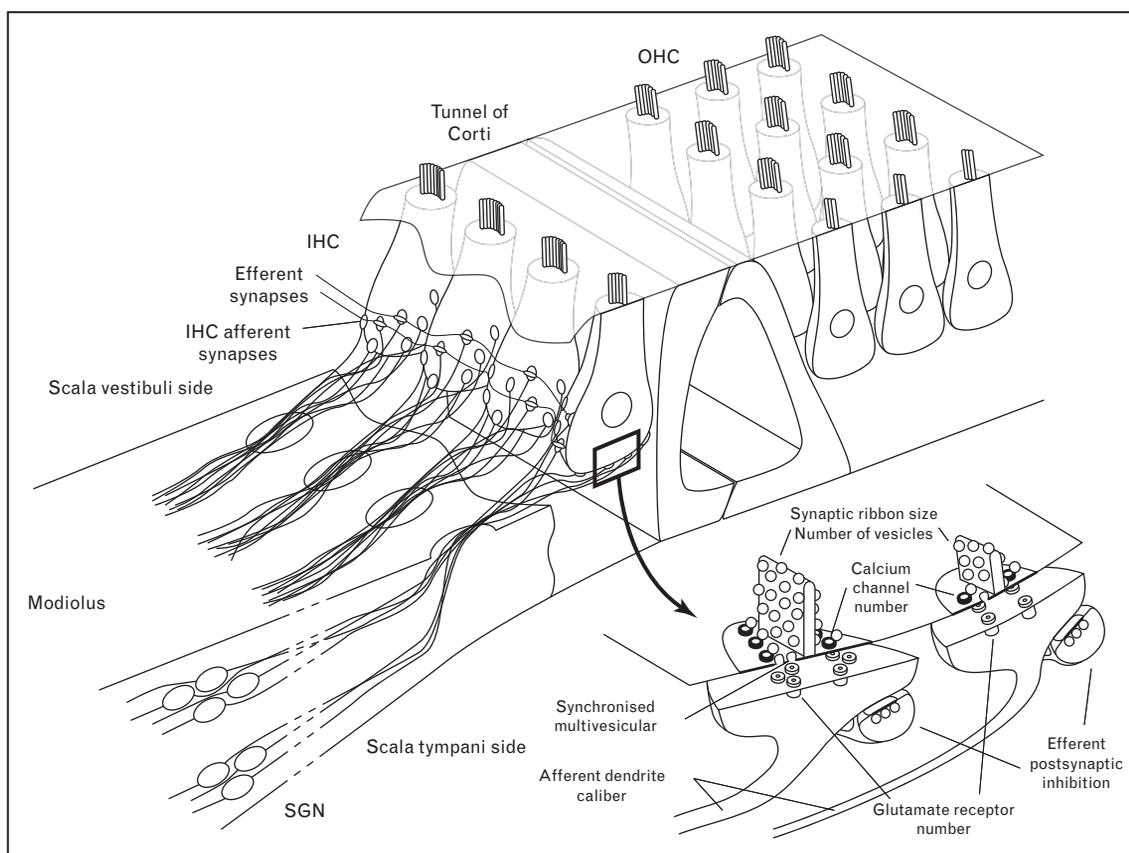
### Heterogeneity in anatomical fiber properties

It has been shown that afferent fibers vary in size and location depending on their characteristic frequency and spiking rate. In cat, in whom this was first studied in detail, fibers clearly separate, with high spiking rate ones

being of larger diameter and originating primarily from the outer IHC side facing the pillar cells and leading through the modiolus close to the scala tympani. Middle and low spiking rate fibers, in turn, originate from the modiolar face and head central near the scala vestibuli [22,31–33]. There has been speculation whether the larger diameter of high spiking rate fibers facilitates action potential initiation and propagation [34], but so far, no conclusive data on this question have been presented.

Although differences in fiber diameter and fiber segregation in the modiolus have been confirmed also in other species (guinea pig [35]; Mongolian gerbil [36]), the latter study failed to identify distinct preferential sites of contact for high or low spiking rate fibers at the circumference of the IHC, as reported in cat. This is in line with a report from mouse, in whom a rather uniform distribution of synapses around the basis of the IHC has been found [20\*\*]. Interestingly, although in mouse and gerbil, auditory fibers also vary significantly in spiking rate, threshold

**Figure 1 Inner hair cell innervation and sources of heterogeneity in afferent fiber spiking behaviour**



In this schematic drawing of the organ of Corti, afferent (radial fiber bundles passing the habenulae perforata) and efferent innervation (parallel fibers forming postsynaptic inhibitory synapses) at the inner hair cells (IHCs) are shown. Spiral ganglion neurons (SGNs) show a tendency to distribute depending on their spiking properties. High-rate, low-threshold fibers are reported to localize preferentially close to the scala tympani side (down). Inset: two afferent IHC ribbon synapses connecting to afferent SGN dendrites. The sources of different spiking properties currently under discussion are illustrated here.

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and diameter, they seem not to fall into distinct spiking rate classes like in cat. They instead show a rather uniform distribution [4,10,37].

##### Synaptic sources of discharge rate heterogeneity

A number of recent morphological and functional studies provide evidence for the afferent IHC synapse being the best candidate source for discharge rate heterogeneity. Indeed, in a classical study, Merchan-Perez and Liberman [38] investigated the ultrastructure of the afferent synapse depending on the spiking properties of the connected fiber. They found that overall morphology and area of contact do not seem to be correlated to spiking rate. However, they were able to show that synapses contacting low or medium spiking rate fibers exhibit larger or even multiple synaptic ribbons and a larger number of synaptic vesicles. There is additional evidence for a diversity of presynaptic ribbon size from a study in which a fluorescent ribbon binding peptide was used to live-label this presynaptic structure in IHCs [39•]. Even more interesting, these authors used live confocal calcium imaging to quantify the  $\text{Ca}^{2+}$  microdomain signals at individual IHC active zones upon depolarization. According to these data, presynaptic sites show substantial heterogeneity in their magnitude of calcium influx as well as their activation voltage even within the same IHC. Differential regulation of the number of presynaptic  $\text{Ca}^{2+}$  channels was suggested as a mechanism for the heterogeneity in the amplitude of synaptic  $\text{Ca}^{2+}$  influx. This hypothesis was supported by a significant variability in the intensity of immunostained synaptic  $\text{Ca}_v1.3$ -channel clusters in these cells and a correlation of  $\text{Ca}^{2+}$  microdomain amplitude and ribbon size estimates. Future work will need to address how a synapse selects its  $\text{Ca}^{2+}$  channel complement and how a differential voltage sensitivity of  $\text{Ca}^{2+}$  influx can be achieved within a small, isopotential cell. Regardless of the mechanism, this presynaptic heterogeneity presents an attractive candidate mechanism for contributing to the differences in postsynaptic response properties. At first glance, an IHC active zone with many  $\text{Ca}^{2+}$  channels and hyperpolarized activation range would be expected to drive a postsynaptic fiber at a high 'spontaneous' spike rate and to increase this rate already at low sound pressure levels. But, as we will discuss later, postsynaptic adaptation of sensitivity might complicate this picture.

Alternatively, one could think of a scenario in which large synapses are able to increase their transmitter release over a wide range of sound intensities, thus elevating – in conjunction with high-sensitivity fibers – the overall dynamic range of the system.

Another mechanism of fiber diversification was suggested based on electrophysiological data. Patch-

clamp recordings from IHC [40,41] and from postsynaptic boutons [42,43] have revealed many important details about the function of transmitter release at this synapse (see [44–46] for detailed reviews). It is believed that one of the differences compared to conventional central synapses is that release of transmitter is from multiple vesicles in a synchronized manner [42,47]. The mechanism for this, however, is still under debate. In a recent publication, Grant *et al.* [48•] showed patch-clamp recordings from postsynaptic boutons of afferent SGN that demonstrated that transmitter release increases its level of synchronization during postnatal development. In newborn rats before the onset of hearing, about half of the excitatory postsynaptic currents (EPSCs) showed visible inflections due to imperfectly synchronized release of several transmitter quanta. In hearing animals, this fraction drops to less than 30%. However, there is substantial variability between fibers, some exhibiting virtually no multiphasic EPSCs, whereas in others, they persistently account for up to 50% of all release events. The authors suggest that at those synapses with poor synchronization, the chance that an EPSC triggers an action potential is inherently lower, making this a candidate mechanism for low spiking rate/high-threshold fibers.

The two hypotheses mentioned before are not mutually exclusive. Future work will need to link  $\text{Ca}^{2+}$  signalling heterogeneity to exocytosis and to identify presynaptic correlates of the observed classes of EPSC amplitude distributions.

The overall responsiveness of a fiber might nevertheless be regulated postsynaptically. In the central nervous system, postsynaptic tuning of neural excitability has been studied in detail (see [49] for a review). One of the key mechanisms either for long-term plasticity (LTP, LTD) or for homeostatic regulation of excitation is the adaptation of postsynaptic receptor density. This mechanism has recently been shown to exist also in postsynaptic boutons of SGN [50•], although its exact function is not yet fully understood. It might not be unlikely that from future studies we learn that also other mechanisms exclusively seen in CNS neurons so far, also play a role at the IHC afferent synapse.

Although changes in the receptor density require minutes to hours, rapid adaptation might also be regulated by efferent innervation via lateral olivocochlear fibers that form synaptic contacts with SGN afferent boutons (see [51] for a review). The latter ones have been shown to modulate activity in auditory nerve fibers [52–54] and seem to primarily innervate low-spiking rate fibers [24]. These connections combined with large presynaptic active zones holding many  $\text{Ca}^{2+}$  channels could offer an interesting means to extend and modulate the

dynamic range of sound encoding by a given spiral ganglion neuron.

## Conclusion

The encoding of sound in the cochlea is governed by a pronounced heterogeneity among auditory nerve fibers. It has become increasingly clear within the last years that the IHC afferent synapse contributes to the generation of this diversity. Several functional elements at the presynaptic and postsynaptic sides have been suggested to be involved, but further studies will be necessary to dissect their precise implication and to estimate their relative importance.

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