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Short review

Sound coding in the auditory nerve of gerbils

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ABSTRACT

Gerbils possess a very specialized cochlea in which the low-frequency inner hair cells (IHCs) are contacted by auditory nerve fibers (ANFs) having a high spontaneous rate (SR), whereas high frequency IHCs are innervated by ANFs with a greater SR-based diversity. This specificity makes this animal a unique model to investigate, in the same cochlea, the functional role of different pools of ANFs. The distribution of the characteristic frequencies of fibers shows a clear bimodal shape (with a first mode around 1.5 kHz and a second around 12 kHz) and a notch in the histogram near 3.5 kHz. Whereas the mean thresholds did not significantly differ in the two frequency regions, the shape of the rate-intensity functions does vary significantly with the fiber characteristic frequency. Above 3.5 kHz, the sound-driven rate is greater and the slope of the rate-intensity function is steeper. Interestingly, high-SR fibers show a very good synchronized onset response in quiet (small first-spike latency jitter) but a weak response under noisy conditions. The low-SR fibers exhibit the opposite behavior, with poor onset synchronization in quiet but a robust response in noise. Finally, the greater vulnerability of low-SR fibers to various injuries including noise- and age-related hearing loss is discussed with regard to patients with poor speech intelligibility in noisy environments. Together, these results emphasize the need to perform relevant clinical tests to probe the distribution of ANFs in humans, and develop appropriate techniques of rehabilitation.

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1. Introduction

Human hearing covers a large range of frequencies (20 Hz–20 kHz) and sound pressure levels (0–120 dB sound pressure level; SPL). Such exquisite frequency sensitivity and sound level encoding is achieved by the sensory hair cells, which act as the auditory transducers of the cochlea. Inner hair cells (IHCs) are innervated by the auditory afferent nerve fibers (ANFs), which in turn convey auditory information to the cochlear nuclei. Frequency sensitivity results from low-level amplification and high-level compression of basilar membrane displacements by outer hair cells (OHCs) (Robles and Ruggero, 2001). Sound level is encoded in the spike rate and timing of the ANFs, driven by a glutamate release from the IHCs (Nouvian et al., 2006).

Pioneer work of functional mapping (Liberman, 1978) demonstrated that three classes of fibers populate the auditory nerve in cats: the high-spontaneous rate (SR) fibers (SR > 18 spikes/s), the medium- (0.5 < SR < 18 spikes/s) and low-SR fibers (SR < 0.5 spike/s). The number of ANFs differs, however, from one species to another, but the classification is relatively homogenous with a majority of high-SR fibers (60–75%) and minorities of medium (15–30%) and low-SR (10–16%) fibers, except in gerbils, where the distribution of ANFs is heterogeneous along the tonotopic axis (Taberner and Liberman, 2005). Based on the fiber characteristic frequency, several authors described two different gerbil cochleae with a majority of high-SR fibers (~74%) below 3.6 kHz and a more balanced distribution of high-, medium- and low-SR fibers above 3.6 kHz (Bourien et al., 2014; Muller, 1996; Ohlemiller et al., 1990, 1991; Schmiedt, 1989). This speciality makes the gerbil's cochlea a unique animal model to probe the functions of different pools of ANFs in the same cochlea (Bourien et al., 2014).

Another advantage of the gerbil model is an anatomical difference to others species. In gerbils, the internal auditory meatus is

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visible through the translucent medial wall of the round window niche (Chamberlain, 1977; Sokolich et al., 1973). In other words, the auditory nerve is just below the round window niche. Therefore, a drug applied into the round window niche can directly access the internal meatus through the thin spongy bone of the medial wall of the round window niche and directly bathes the auditory nerve. Indeed, application of the Na-K-ATPase inhibitor ouabain ablates the ANFs in a dose-dependent manner from low-to high-SR fibers (Bourien et al., 2014). This specificity may explain the greater ouabain-sensitivity in gerbils (100 μM (Bourien et al., 2014)) than in mice (1 mM (Chambers et al., 2016)) and rats (1 mM (Fu et al., 2012)) to reach a near-complete cochlear denervation.

Because of these special features of the gerbil's cochlea, we focus this review on the functional properties of the ANFs in gerbils in quiet and noisy environments. To update knowledge on sound coding in the auditory nerve of gerbils, we re-analyzed and completed our data set of single unit recordings published in Bourien et al. (2014) and discuss them in the context of the relevant literature.

2. Functional mapping of auditory nerve fibers in gerbils

The methods to record single fibers of auditory nerve in gerbils were extensively described by Bourien et al. (2014). Briefly, the surgical approach to the auditory nerve was through the posterior fossa after a craniotomy. Single units ($n = 1005$ fibers) from the auditory nerve were recorded in 44 adults gerbils (2–6 months old). Once a fiber was isolated, its characteristic frequency (CF) and threshold values were determined from the tip of the tuning curve, and the fiber spontaneous rate (SR) was calculated over a 30-s sample.

2.1. Properties of auditory nerve fibers according to their CF and SR

To visualize the frequency range of gerbil hearing, we plotted the threshold of each fiber as a function of its CF using a color scale to indicate the fiber SR (Fig. 1A). Consistent with previously reported data (Muller, 1996; Ohlemiller et al., 1990; Schmiedt, 1989), CFs were distributed from 0.25 to 50 kHz (median value at 4.75 kHz) and the thresholds ranged from 0 to 50 dB SPL (median value at 15 dB SPL, Fig. 1A). The threshold distribution per octave band was relatively homogeneous from 1 to 16 kHz (see percentile values in Fig. 1A) but tended to shift rapidly below 1 kHz and above 16 kHz towards higher sound levels. Interestingly, the 10th percentile fits remarkably the behavioral audiogram (Ryan, 1976), suggesting that a small fraction of fibers may be responsible for the auditory threshold. The SR distribution of fibers was also very broad, with 95% of fibers ranging from 0.03 to 100 spikes/s (~4 decades of dynamic range, see color scale in Fig. 1A).

An analysis of the CF distribution per half-octave band (Fig. 1B) shows a clear bimodal shape (with a first mode around 1.5 kHz and second around 12 kHz) and a notch in the histogram near 3.5 kHz. This feature appears to be specific to the gerbil auditory nerve; it was observed whatever the nature of the searching stimulus (*i.e.* electric shocks (Ohlemiller and Echteler, 1990), or acoustic broadband noise (Bourien et al., 2014)) and the surgical approach that had been used to expose the auditory nerve (*i.e.* round window, (Muller, 1996; Ohlemiller et al., 1990); or dorsal approach (Bourien et al., 2014)). To determine the frequency location of the notch, two statistical methods were used; a fit with a double Gaussian model and an agglomerative, ascending clustering of fibers calculated from *log(CF)* (Fig. 1B). The two approaches attest to the presence of a notch located at 3.5 kHz. Considering fibers with a CF below or above 3.5 kHz, the distribution of SR differs significantly between the two groups (Fig. 1C). For CF fiber below 3.5 kHz (i.e. towards the apical part of the cochlea), the SR histogram is bimodal as reported in cats (Liberman, 1978), guinea pigs (Tsuji and Liberman, 1997), chinchillas (Relkin and Doucet, 1991), rabbits (Borg et al., 1988) and ferrets (Sumner and Palmer, 2012). Above 3.5 kHz, the distribution of SR is almost unimodal as observed in mice (Taberner and Liberman, 2005) and rats (el Barbary, 1991). The mean SR value in the low-CF group (39 spikes/s ± 27.3, mean ± SD) is twice as large as in the high-CF group (19.5 spikes/s ± 25.2, $p < 0.001$, Wilcoxon test, Fig. 1C). The examination of the relationship between threshold and SR (Fig. 1D) confirms that the classical negative correlation between threshold and SR (Liberman, 1978) is maintained in both groups (low-CF: slope = −6.5 dB per decade of SR; high-CF: slope = −5 dB per decade of SR).

2.2. Characteristics of the rate-intensity functions

For a subset of 418 fibers, the rate-intensity functions were recorded using tone bursts at CF (1-ms rise time, 50-ms duration, 10 bursts/s) over a range of stimulus levels (0–80 dB SPL in 4 dB steps, 60 presentations per level, random level order). Fig. 2A shows a set of rate-intensity functions for fibers pooled per octave band according to CF. The rate-intensity functions of low-CF fibers (CF ≤ 3.5 kHz, orange panels) seem similar in terms of threshold, sound-driven rate and steepness, in contrast to fibers with higher CF (purple panels). To further examine this, a fitting model (Heil et al., 2011) was applied to each rate-intensity function to estimate the saturation rate (Figs. 2B, C), sound-driven rate (Figs. 2D, E), maximum slope as a proxy of the steepness (Figs. 2F, G), and dynamic range (Figs. 2H, I). Consistent with Ohlemiller et al. (1991), the value of these indicators changes significantly from low-to high-CF fibers, except for the dynamic range (Figs. 2H, I). Below 3.5 kHz, the sound-driven rate (Fig. 2D) and maximum slope (Fig. 2F) were 123 ± 39 spikes/s and 7.9 ± 3 spikes/s/dB (mean ± SD), respectively. Above 3.5 kHz, the sound-driven rate is higher (198 ± 52 spikes/s, $p < 0.001$, Wilcoxon test) and the slope of the rate-intensity function is steeper (19.7 ± 8.8 spikes/s/dB, $p < 0.001$, Wilcoxon test), with, however, a greater variability related to the mixture of both low and high spontaneous rate fibers (Winter et al., 1990). Based on the different pools of fiber distributions, it is worth noting that the low-frequency region of the gerbil cochlea resembles that of species that also have sensitive low-frequency hearing (*e.g.* cats, guinea pigs, rabbits, chinchillas, ferrets), whereas the basal part resembles more data from species with only high-frequency sensitivity like mice and rats.

These findings show that in gerbils, the characteristics of rate-intensity functions vary considerably with CF in contrast with other animal models (cats: (Palmer and Evans, 1980); guinea pigs: (Winter et al., 1990); mice (Taberner and Liberman, 2005):), where the shape of rate-intensity functions rather depends on SR (see Heil and Peterson (2015) for a review). Taking the guinea pig as an example, the rate-intensity functions of high-SR fibers are described as flat-saturating curve whereas rate-intensity functions of medium- and low-SR fibers are more sloping-saturating or even straight (Winter et al., 1990). This specificity may be explained by the biophysical properties of IHCs of gerbils (Johnson, 2015) in which apical IHCs (CF~0.3 kHz) have significantly more depolarized resting membrane potentials, faster kinetics, and shorter membrane time constants than high-frequency cells (~30 kHz). The faster kinetics of low-frequency IHCs allow them to follow the phasic components of sound (phase locking coding), which is not required for high-frequency cells that are instead optimally configured to encode sustained, graded responses. In a comprehensive review discussing how ion transport proteins in hair cells work to produce a sensitive hearing organ, Patuzzi (2011) speculated that the apical part of the mammal cochlea, that mainly uses neural phase locking, may benefit from having a majority of high-