Research Article

The Polarity Sensitivity of the Electrically Stimulated Human Auditory Nerve Measured at the Level of the Brainstem

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ABSTRACT

Recent behavioral studies have suggested that the human auditory nerve of cochlear implant (CI) users is mainly excited by the positive (anodic) polarity. Those findings were only obtained using asymmetric pseudomonophasic (PS) pulses where the effect of one phase was measured in the presence of a counteracting phase of opposite polarity, longer duration, and lower amplitude than the former phase. It was assumed that only the short high-amplitude phase was responsible for the excitation. Similarly, it has been shown that electrically evoked compound action potentials could only be obtained in response to the anodic phases of asymmetric pulses. Here, experiment 1 measured electrically evoked auditory brainstem responses to standard symmetric, PS, reversed pseudomonophasic, and reversed pseudomonophasic with inter-phase gap (6 ms) pulses presented for both polarities. Responses were time locked to the short high-amplitude phase of asymmetric pulses and were smaller, but still measurable, when that phase was cathodic than when it was anodic. This provides the first evidence that cathodic stimulation can excite the auditory system of human CI listeners and confirms that this stimulation is nevertheless less effective than for the anodic polarity. A second experiment studied the polarity sensitivity at different intensities by means of a loudness balancing task between pseudomonophasic anodic (PSA) and pseudomonophasic cathodic (PSC) stimuli. Previous studies had demonstrated greater sensitivity to anodic stimulation only for stimuli producing loud percepts. The results showed that PSC stimuli required higher

amplitudes than PSA stimuli to reach the same loudness and that this held for current levels ranging from 10 to 100 % of the dynamic range.

Keywords: cochlear implants, objective measures, psychophysics, polarity sensitivity, electrically evoked auditory brainstem responses, asymmetric pulse shapes, EABR

INTRODUCTION

During the past years, polarity sensitivity of the electrically stimulated human auditory nerve (AN) has been investigated in order to optimize the design of pulse shapes for improved performance with a cochlear implant (CI).

Contrary to most data obtained from animal and computer models (Frijns et al. 1996; Miller et al. 1997, 1998, 1999b, 2001; Klop et al. 2004; Smit et al. 2010), objective and behavioral data from CI users suggest that the anodic polarity is more effective than the cathodic one (Macherey et al. 2006; 2008, 2010, 2011; Undurraga et al. 2010, 2012). However, there are several issues that shall be taken into account from those studies.

First, all behavioral data were obtained in the presence of a counteracting phase of opposite polarity (Macherey et al. 2006; 2008; 2010; 2011). A number of studies have shown that thresholds decrease between 2 and 7.5 dB per doubling of phase width (PW) (Bonnet et al. 2012; McKay and McDermott 1999; Miller et al. 1999a; Moon et al. 1993; Pfingst et al. 1991; Prado-Guitierrez et al. 2006; Shepherd and Javel 1999; Zeng et al. 1998). Moon et al. (1993) found that

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thresholds measured in human CI users for PW longer than 0.5 ms decreased 5.71 dB/doubling of PW for single pulses and 7.54 dB/doubling for pulse trains presented at 100 pps. Similarly, Bonnet et al. (2012) reported that thresholds decreased about 6.46 dB/doubling of PW at higher rates (≥ 774 pps). Therefore, the percept of pseudomonophasic cathodic (PSC) stimuli could arise either from the short-high cathodic phase or from the long-low anodic phase (see Fig. 1).

Macherey et al. (2008) measured masking by anodic and cathodic phases of pseudomonophasic (PS) pulses with an inter-phase gap (IPG) of a symmetric (SYM) biphasic probe and found that the anodic phase produced more masking than the cathodic phase. However, it has been suggested that different polarities could excite different populations of AN fibers (Miller et al. 1997; Ranck 1975). Thus, it is possible that the high masking effectiveness of the anodic phase was due to a greater overlap of those fibers excited by the anodic masker and the SYM probe than those fibers excited by the cathodic phase. In addition, although some masking was produced when the short-high cathodic phase preceded the probe, it was not known whether this was produced by that cathodic phase or instead resulted from earlier anodic stimulation. Similarly, PS stimuli are louder when the short-high phase is anodic (pseudomonophasic anodic, PSA) than cathodic (PSC), but it is not known whether the fact that listeners hear the PSC stimulus at all is due to the

short-high cathodic phase or to the long-low anodic phase. Evidence consistent with the idea that CI listeners are insensitive to cathodic stimulation comes from measures of the electrically evoked compound action potential (ECAP). Those studies, which used the masker-probe paradigm (Macherey et al. 2008; Undurraga et al. 2010, 2012), found evidence for activation only by the anodic phase of asymmetric pulses.

However, it is possible that cathodic responses were not detected due to the characteristics of the effective place of excitation across and along the AN fibers. If different polarities excite either different population of neurons (Miller et al. 1997; Ranck 1975) or different sites along the same AN fibers (e.g., the cathodic polarity excites more peripherally and the anodic polarity more centrally (Miller et al. 1999c, 2004; Rattay et al. 2001)), or both different population and different sites, the absence of ECAP responses to cathodic pulses may be explained by the effect of those specific polarity-dependent responses of the electrically stimulated AN. For example, if a cathodic pulse is exciting, effectively, far away from the recording electrode, ECAP responses could be very small or absent.

In a previous study, spread of excitations measured with asymmetric and SYM maskers with a long IPG in bipolar (BP) mode produced more excitation (large ECAP amplitudes) close to the masker electrode that delivered the effective anodic stimulus (Undurraga et al. 2012). This finding agrees with pitch differences observed with bipolar PS pulses of opposite polarities where the pitch was lower when the apical electrode of the channel delivered the PSA waveform (Macherey et al. 2011). However, the study by Miller et al. (1999c) in cats suggests that the anodic phase (with high thresholds) excites the AN at the central axon in a highly synchronized fashion, whereas the cathodic phase (with low thresholds) excites at the peripheral processes where the degree of synchronization was low and depended upon stimulus amplitude. Thus, ECAP responses may mainly reflect the activity of highly synchronized spikes elicited by the anodic phase while spikes elicited by the cathodic phase may just be too asynchronous to be detected.

Moreover, the status of the peripheral processes may increase the temporal jitter among spikes of different AN fibers. If the cathodic polarity is exciting at the peripheral level, it is possible that the anatomical properties of peripheral processes (degree of myelination and/or length) have a high variance in comparison to central axons. Since the degeneration of the AN is usually accompanied by partial (decrease of myelination) or total peripheral degeneration (Fayad and Linthicum 2006; Hinojosa and Marion 1983; McFadden et al. 2004; Nadol 1997; Nadol et al.

FIG. 1. Overview of pulse shapes. *Top:* symmetric cathodic first (SYMC), pseudomonophasic cathodic (PSC), reversed pseudomonophasic cathodic (RPSC), and reversed pseudomonophasic cathodic with an inter-phase gap (RPSC-IPG). *Bottom:* symmetric anodic first (SYMA), pseudomonophasic anodic (PSA), reversed pseudomonophasic anodic (RPSA), and reversed pseudomonophasic anodic with an inter-phase gap (RPSA-IPG). Time zero used in each EABR is indicated by the red vertical dotted line.

2001; Shepherd and Hardie 2001; Zhou et al. 1995), a large variance of the anatomical characteristics of peripheral processes is expected. A decrease of myelination will increase the time constant of the neural membrane (Koles and Rasminsky 1972; Tasaki 1955). Therefore, a large variability in the degree of myelination across peripheral fibers may result in reduced neural synchrony or in increasing temporal jitter. A similar temporal jitter could be expected from a large variance of electrode–neuron distance (Mino et al. 2004). If so, ECAP responses may not be suitable to detect the activity of peripheral process fibers.

Additionally, ECAP responses may suffer from a potential ambiguity. The recordings may contain the neural response traveling not only towards the central auditory system (orthodromically), but also in the opposite direction towards the peripheral processes (antidromically) (Briaire and Frijns 2005; Brown 1994; Miller et al. 2004; Rattay et al. 2001). Briaire and Frijns (2005) suggested that ECAP responses may preferentially reflect the activity of antidromic spikes depending on the position of the stimulating and recording electrodes. It is therefore possible that cathodic pulses elicit action potentials propagating towards the central auditory system but that they are not registered during ECAP measurements due to the absence of antidromic spikes.

The aims of a first experiment were:

1. To examine whether the previous evidence (Macherey et al. 2008, 2010, 2011; Undurraga et al. 2010, 2012) that the anodic is the most effective polarity was caused by the short-high anodic phase of a PS pulse
2. To determine whether polarity effects depend on the stimulation level, and
3. To examine whether the cathodic phase can excite the AN

These were studied by means of electrically evoked auditory brainstem responses (EABRs) obtained at different stimulation levels. EABRs monitor the compound activity triggered by more central neural generators, and therefore, they may be able to capture the neural activity that cannot be observed by means of ECAP responses. The aim of a second experiment was to determine the range of levels over which the greater sensitivity to anodic stimulation occurs. Loudness balancing studies have found that, for example, PSA stimuli are louder than PSC stimuli at levels corresponding to “most comfortable loudness,” but this difference does not occur at threshold (Macherey et al. 2006). Similarly, Macherey et al. (2010) measured behavioral excitation patterns produced by SYM and PS stimuli in bipolar mode. They found that excitation patterns were higher closer to the electrode of the bipolar channel that delivered

the PSA stimuli. However, no polarity differences were observed when an IPG of 4.3 ms was added. A plausible explanation for this lack of polarity differences is that polarity effects are level dependent. In those studies, polarity effects for PSA and PSC were found at comfortable level (CL). Since stimuli with long IPGs require less current to evoke the same loudness than stimuli with short IPGs (Carlyon et al. 2005; Macherey et al. 2006; McKay and Henshall 2003; van Wieringen et al. 2005; 2006), it has been suggested that PS stimuli with an IPG were presented at levels at which polarity has no effect (Macherey et al. 2010). We therefore compared the loudness of PSA and PSC stimuli, using a loudness balancing procedure, over a wide range of stimuli.

METHODOLOGY

Subjects

Four users of the CII or HiRes90k CI (Advanced Bionics) took part. All had been implanted with the HiFocus I or HiFocus II electrode array, which consists of 16 contacts (1 to 16 in an apical-to-basal order) with a center-to-center spacing between adjacent electrodes of 1.1 mm. Testing was approved by the Medical Ethics Committee of the UZLeuven/KULeuven (approval number B32220072234), and informed consent was obtained from all subjects. Details of subjects regarding their age, etiology, duration of deafness (DD), duration of CI use, and implantable cochlear stimulator (ICS) are given in Table 1.

EABR stimuli

An overview of the different waveforms is shown in Figure 1. EABR responses were measured by using four different charge balanced stimuli: SYM, PS, reversed pseudomonophasic (RPS), and reversed pseudomonophasic with an inter-phase gap (RPS-IPG).

SYM pulses were used as control since we expected little or no polarity effect in comparison to PS, RPS, and RPS-IPG stimuli. PS and RPS pulses were included to test whether the short-high or the long-low phase of these stimuli is the effective one. PS pulses had a second phase of opposite polarity that was eight times longer and smaller than the first phase. RPS pulses are similar to PS pulses but with the long-low phase followed by the short-high phase of opposite polarity. It was expected that EABRs would be time locked to the most effective phase. RPS-IPG is similar to the RPS stimulus but with a long IPG of 6 ms. This long IPG was added to allow recordings of EABR responses to the last phase of the stimuli with little

TABLE 1

Bibliographical data of the subjects, including age, DD, etiology, time of CI use, and ICS

Subject	Age (years)	Etiology	DD (years)	CI (years)	ICS
S1	66	Unknown progressive	4	8	CII
S2	58	Congenital progressive	7	7	HiRes90K
S3	58	Unknown progressive	1	6	HiRes90K
S4	64	Meningitis	6	7	HiRes90K

effect of the initial low phase (e.g., Cohen 2009; Miller et al. 2001; Morsnowski et al. 2006). Since the more prominent EABR peaks are normally within the first 5 ms after the onset of a stimulus, this IPG is long enough to prevent possible effects of responses elicited by the first phase, under the assumption that the short phase would be able to stimulate the AN.

SYM, PS, and RPS were delivered after 12 ms of null stimulation (pulses with zero amplitude). RPS-IPG pulses were delivered after 6 ms of null stimulation so that the second phase was also delivered 12 ms after the onset of stimulation. The purpose of this initial null stimulation was to avoid overlap of RF artifacts with the EABR. Saline and resistive recordings performed in our lab had indicated that these RF artifacts lasted up to 10–11 ms from the onset of stimulation.

Stimuli were delivered at a rate of 21 pps in monopolar mode through an electrode in the middle of the array (electrode 9). For all stimuli, the PW was 75 μ s (600 μ s for the long-low phase of asymmetric stimuli). Stimulus polarity was alternated in order to decrease across-polarity time variance due to other factors such as electrode impedances or background noise variations and muscular artifacts. Responses to each polarity were averaged independently of each other. In this way, external factors should affect the responses to both polarities in a similar way. Thresholds and comfortable levels were determined prior to EABR recording.

Stimuli were delivered at different intensities, in approximately five to seven steps, between threshold and comfortable levels in order to obtain amplitude growth functions. A minimum of 4,000 sweeps per polarity were recorded. Time zero was defined as the onset of the first phase for SYM, PS, and RPS stimuli and as the onset of the second phase for an RPS-IPG stimulus (see Fig. 1). The time position of each phase was determined precisely from the stimulation information sent to the CI device.

EABR recording

Stimuli were generated and responses recorded by custom software created in our laboratory (Hofmann and Wouters 2010). The stimuli were transmitted to

the Clinical Programming Interface (CPI). The CPI sent the pulse table (which contains all stimulation information such as pulse shape, PW, and rate) to the Platinum Sound Processor (PSP) and generated trigger pulses for each stimulus. The PSP transmitted each stimulus to the implanted CI. The recording setup is illustrated in Figure 2.

EABRs were recorded from surface electrodes placed on the head of the subjects in accordance with the International 10–20 system. The reference (negative) electrode was placed on the ipsilateral mastoid (TP9 or TP10) relative to the side of the implanted CI. The active (positive) electrode was placed on the vertex (Cz), and the ground electrode was placed on the contralateral mastoid (TP9 or TP10). Responses were amplified through a Jaeger-Toennies eight-channel low-noise differential medical preamplifier with a gain of 50,000. The cutoff frequencies of the internal bandpass filter (6 dB/octave) of the amplifier were set to 2 and 20,000 Hz, respectively. The amplified response and the trigger signal (coming from the CPI) were recorded by an external RME Hammerfall DSP Multiface II sound card at a sampling frequency of 96 kHz and with resolution of 24 bits/sample. All measurements were performed in an electrically isolated Faraday sound booth, and electrode impedances were kept below 5 k Ω . During the measurements, subjects lay on a couch as quietly as possible.

Post-processing

EABRs were processed with a custom interface developed in Matlab. The post-processing chain involved a series of steps. First, since stimuli were presented in alternating polarity, trigger detection is crucial to ensure that averaged responses effectively represent each polarity. In the case of any missing or undetected trigger pulse during the averaging process, the final traces would result in mixtures of waveforms containing both polarities. To ensure that both polarities were properly averaged, the raw waveforms detected with each trigger pulse were analyzed by using a matched filter that compared each of the responses with a template (the first sweep). As each sweep contained a relatively small

FIG. 2. Schematic diagram of the measurement setup. Stimuli are generated with our custom software (RBA) which controls the CPI. The CPI sends the trigger pulses to the RME sound card and the pulse table to the PSP that further sends the stimulation information to the implanted CI. Evoked EABRs are amplified and sent to the RME sound card. Responses are then stored and averaged by the RBA software.

biological wave in comparison with the electrical artifact, electrical artifacts were used to check the polarity of each sweep during the averaging process. As a detection criterion, the matched filter used a correlation coefficient of $+0.9$ or -0.9 : if the correlation of the incoming sweep with the template was positive and greater than 0.9 (current sweep similar to the template), it was averaged in one polarity group (anodic). If the correlation between the incoming sweep and the template was less than -0.9 , the sweep was averaged in the second polarity group (cathodic).

The second step consisted of canceling the electrical artifact that contaminated the response. Figure 3 shows the raw traces for SYM, PS, and RPS-IPG pulse shapes for both polarities. It is observed that PS and particularly RPS-IPG stimuli presented current flows containing the opposite polarity of the preceding stimulus phase. This current flow was due to the passive discharge of the DC-blocking capacitors coupled to each of the electrodes of the array that prevent the accumulation of charge in the cochlea

(Carlyon et al. 2005; Macherey et al. 2006). As it is shown, the scale of the electrical artifact due to both stimuli (about $200 \mu\text{V}$) and current flow (a maximum of about $30 \mu\text{V}$) is large in comparison with the biological response of which the amplitudes are in the order of 0.5 to $1 \mu\text{V}$. Note that the stimulus artifact is presumably higher than $200 \mu\text{V}$ because this value corresponds to the maximum input range of the recording device.

Thus, in order to cancel the electrical artifact that depends on the pulse shape, an exponential function was fitted (see Eq. 1) from 1.0 until 12 ms after the onset of the stimuli. This fitting is also illustrated in Figure 3 (blue lines).

$$f(t) = a_0 + a_1 \cdot e^{(-a_2(t-t_0))} \quad (1)$$

Once fitted, the template was subtracted from the response. Next, responses were blanked usually from the beginning of the recording up to 1.5 to 2 ms.

FIG. 3. Unprocessed traces obtained with SYM, PS, and RPS-IPG pulse shapes from subject S1. The *top panel* shows the traces corresponding to one polarity, and the *bottom panel* shows the traces corresponding to the opposite polarity. The stimulation amplitude and the pulse shape are indicated in each figure. *Blue lines* show the fitted exponential function.

Furthermore, the noise was reduced by using a zero-phase digital filter (bandpass fourth-order Butterworth filter) with cutoff frequencies set to 300 and 3,000 Hz. The processed traces were averaged by using weighted averaging (Don and Elberling 1994; Elberling and Don 1984; Elberling and Wahlgreen 1985; Silva 2009). Under this method, the variance of the noise can be estimated by tracking one or several fixed points over time for subsets of sweeps, e.g., each 32 sweeps. Since the variance of each block is known, the final waveform is obtained by weighting each subset by the inverse of its variance. This method prevents the effect of nonstationary noise and provides an estimation of the post-average residual noise (RN) which is estimated from the variance of fixed points along time sampled from each recorded sweep.

In this study, the power (or standard deviation) of the RN ($\hat{\sigma}_{RN}$) was estimated by tracking eight points from each sweep placed from 2 to 9 ms after the onset of the stimuli (for details, refer to Don and Elberling 1994). Each subset of sweeps consisted of a minimum of 32 sweeps, and the size of the final subset was determined adaptively by comparing the variance of successive subsets (Silva 2009).

EABR responses were characterized by the latencies and the amplitudes of peaks III and V. For CI patients, peak III, which is generated by the cochlear nucleus, occurs approximately 2 ms after the onset of the stimulus, whereas peak V, which is generated by the lateral lemniscus–inferior colliculus (e.g., Legatt 2002; Møller et al. 1995), occurs approximately 4 ms after the onset of the stimulus. Latency was defined as the time position of the respective peaks. The amplitude was defined as the difference between the positive peak and the following trough (see Fig. 4). Amplitude variances were estimated as $\hat{\sigma}_{amp}^2 = 2\hat{\sigma}_{RN}^2$ (this value corresponds to the uncorrelated sum of the noise variance associated to each point).

Figure 4 shows the final traces without (top) and with (bottom) the exponential subtraction. It is shown that removal of the electrical artifacts was essential to avoid the distortions that overlap the EABRs obtained with PS, RPS (not plotted), and RPS-IPG stimuli. Note that the RN (shown by horizontal lines that represent $\pm 2\hat{\sigma}_{RN}$) serves as a visual reference to determine when a point was significantly higher than the RN.

Loudness balancing task

PSA and PSC stimuli with an amplitude ratio between phases of 8 were loudness balanced at a range of levels by using the APEX software platform (Laneau et

al. 2005). The phase duration of the short-high phase was 32 μ s, and stimuli were presented at a pulse rate of 98 pps. First, loudness balancing was performed with the PSC stimulus (reference) fixed at 10, 20, 30, 40, 50, 60, 70, 80, and 90 % of its dynamic range (DR), and the subjects were allowed to increase or decrease the PSA stimulus (signal) until both reference and signal were perceived equally loud. Second, the roles of the PSC and PSA stimuli were reversed, i.e., the PSA stimulus was the reference and the PSC stimulus was the signal. For each reference amplitude, balancing measurements were repeated six times, and the signal had different starting amplitudes each time. Signal and reference had a duration of 400 ms and were presented with an interval of 500 ms.

Statistical analyses

In order to analyze and compare the overall effects of amplitudes and latencies of responses, factor analyses were performed by using linear mixed-effects (LME) models. LME models were chosen since they can deal with unbalanced data, complex modeling of random effects variables, and can account for nonsphericity (Baayen et al. 2008; Krueger and Tian 2004; Newman et al. 2011; Wierda et al. 2010).

LME analyses were performed using the R software package (Development Core Team 2011) and the R packages lme4 (Bates et al. 2012), languageR (Baayen 2012), and LMERConvenienceFunctions (Tremblay 2012). Normality and homogeneity were checked by visual inspection of plots of residuals against fitted values. For all LME models in this study, the factor subject was set at random. The initial model included a random interaction between the fixed continuous factor (stimulation amplitude) and the random factor subject. After the initial LME model was fitted (including complex random effects structures), the model was simplified by removing nonsignificant factors by means of likelihood ratio tests. In order to validate the final LME model, we performed likelihood ratio tests comparing the models with fixed effects to the null model that only contained the random effects.

The p values obtained from LME models were obtained by performing 50,000 Markov-chain Monte Carlo (MCMC) samplings (see, e.g., Andrieu et al. 2003) which are more conservative than those based on t distributions. The significance level was $\alpha=0.05$.

Note that degrees of freedom are not reported since the simple formulas for the degrees of freedom for inferences based on t or F distributions do not apply to LME models with small samples (Baayen et al. 2008).

FIG. 4. EABR responses obtained without exponential subtraction (*top*) and after exponential subtraction (*bottom*) for SYM, PS, and RPS-IPG, respectively. The stimulation amplitude and the pulse shape are indicated in each figure. Peaks III and V are also shown for the responses in the *bottom* panel. The horizontal lines show $\pm 2\hat{\sigma}_{RN}$.

RESULTS

EABR responses to SYM stimuli

EABR responses obtained with SYM stimuli from two subjects are shown in Figure 5. Responses obtained with symmetric anodic first (SYMA) (black lines) and with symmetric cathodic first (SYMC) (red lines) are shown as a function of the current amplitude in the

left panel. Amplitudes for peaks III and V are shown in the middle and right panels, respectively. Note that peak V of subject S1, at the highest stimulation level, was superimposed by, presumably, a myogenic response (e.g., Fifer and Novak 1990). This measure was not included in the statistical analysis. Figure 5 shows that responses were very similar for both waveforms for most of the stimulation amplitudes across subjects.

FIG. 5. EABRs to SYMA (black) and to SYMC (red) from two subjects. The *left* panel shows the obtained responses, whereas the *middle* and the *right* panels show the amplitude growth functions of peaks III and V, respectively. Horizontal lines show $\pm 2\hat{\sigma}_{RN}$. The error bars on amplitude growth functions correspond to $2\hat{\sigma}_{amp}$. Asterisks denote significant differences between the responses.

Amplitudes. To investigate which factors explain the variability of the amplitudes, we fitted an LME model with fixed factors peak (III and V), %DR, and polarity (SYMA and SYMC). Results indicate that the factor peak ($p < 0.001$), %DR, and the interaction between factor peak and %DR ($p = 0.007$) were significant. At higher stimulation levels, the amplitude was higher for peak III than for peak V. However, at lower stimulation levels, amplitudes were similar for both peaks. The factor polarity was not significant.

Latencies. Figure 6 summarizes the latencies for each pulse shape and polarity as a function of the percentage of the DR for all subjects. Latency differences between SYMA and SYMC responses were observed across stimulation levels (see also Fig. 5).

The fitting of an LME model with polarity (SYMA and SYMC), peak (III or V), and %DR as fixed factors indicated that all factors were significant ($p < 0.01$). Interactions were not significant. The model indicated that the latency of the SYMA response was 80 μ s ($se = 13$ μ s) shorter than the latency of the SYMC response and similar to the PW (75 μ s), suggesting that the SYM response was elicited by the anodic phase of the stimulus. The latency difference between peaks III and V was 1.73 ms ($se = 13$ μ s). The slope of the factor %DR was negative, indicating that latencies decreased when the stimulation amplitude increased. This can be observed in Figure 6, where regression

line slopes are slightly negative for most of the subjects and pulse shapes.

EABR to asymmetric pulses

Amplitudes. Figures 7, 8, and 9 show EABRs from two subjects obtained with PS, RPS, and RPS-IPG pulse shapes, respectively. Responses to anodic pulses (PSA, RPSA, reversed pseudomonophasic anodic with an inter-phase gap (RPSA-IPG)) are shown in black, whereas responses to cathodic pulses (PSC, reversed pseudomonophasic cathodic (RPSC), reversed pseudomonophasic cathodic with an inter-phase gap (RPSC-IPG)) are shown in red. Note that for subject S1, all EABRs were superimposed by myogenic responses at higher stimulation levels. These measurements were not included in the statistical analyses.

EABRs to all pulse shapes and from all subjects showed higher amplitudes when the short-high phase was anodic than cathodic (indicated by the asterisks). More interestingly, Figure 9 shows that EABRs to RPS-IPG stimuli were obtained for both polarities, demonstrating that both polarities (without a preceding phase of opposite polarity) can excite the AN. Moreover, EABRs for all asymmetric pulse shapes were similar (visual inspection), suggesting that PS and RPS stimuli elicited responses that resembled those obtained with RPS-IPG stimuli, the ideal “monophasic” case.

Interestingly, EABRs for subject S2 (not shown) could only be obtained with the anodic pulse shapes, i.e., PSA (both peaks III and V were observed), RPSA (both peaks

FIG. 6. EABR latencies of peaks III (top panel) and V (bottom panel), respectively. Latencies for SYMA, PSA, RPSA, and RPSA-IPG responses are shown in black, whereas for the opposite polarity, they are shown in red. Lines show the best linear fitting for each pulse shape and polarity.

FIG. 7. EABRs to PSA (black) and to PSC (red) from two subjects. The left panel shows the obtained responses, whereas the middle and the right panels show the amplitude growth functions of peaks III and V, respectively. Horizontal lines show $\pm 2\hat{\sigma}_{RN}$. The error bars on amplitude growth functions correspond to $2\hat{\sigma}_{amp}$. Asterisks denote significant differences between the responses.

III and V were observed), and RPSA-IPG (only peak V was observed). Likewise, EABRs to RPS-IPG stimuli from

subject S3 were only obtained for the anodic polarity, i.e., the RPSA-IPG stimulus (only peak V was observed).

FIG. 8. EABRs to RPSA (black) and to RPSC (red) from two subjects. The left panel shows the obtained responses, whereas the middle and the right panels show the amplitude growth functions of peaks III and V, respectively. Horizontal lines show $\pm 2\hat{\sigma}_{RN}$. The error bars on amplitude growth functions correspond to $2\hat{\sigma}_{amp}$. Asterisks denote significant differences between the responses.

FIG. 9. EABRs to RPSA-IPG (black) and to RPSC-IPG (red) from two subjects. The *left panel* shows the obtained responses, whereas the *middle* and the *right panels* show the amplitude growth functions of peaks III and V, respectively. *Horizontal lines* show $\pm 2\hat{\sigma}_{RN}$. The *error bars* on amplitude growth functions correspond to $2\hat{\sigma}_{amp}$. *Asterisks* denote significant differences between the responses.

In order to evaluate whether the position of the long-low phase in PS and RPS pulses produced a significant effect on the amplitudes of the evoked responses and whether they differed significantly from RPS-IPG responses (the ideal “monophasic” case), amplitudes of all these responses were compared. We fitted an LME model with fixed factors pulse shape (PS, RPS, and RPS-IPG), peak (III or V), %DR, and polarity (anodic or cathodic). Results indicated that factors peak ($p < 0.001$) and polarity ($p < 0.001$) were significant. Interactions between %DR and peak ($p < 0.001$) as well as between peak and polarity ($p = 0.003$) were significant. The factor pulse shape was not significant, indicating that the responses elicited by these three different pulse shapes were similar.

Figure 10 shows the interaction between peaks and polarity. For both peaks (III and V), amplitudes of anodic responses were higher than amplitudes of cathodic responses. The mean amplitude difference between anodic and cathodic responses measured at peak III was $0.31 \mu\text{V}$ (7.2 dB), whereas this difference measured at peak V was $0.18 \mu\text{V}$ (5.4 dB). The average polarity difference across peaks was $0.24 \mu\text{V}$ (6.4 dB).

The interaction between %DR and peak was similar to that obtained with SYM pulses, where peak III amplitude was higher than peak V at higher stimulation levels, but very similar at lower stimulation levels.

Latencies. EABRs to RPS-IPG demonstrated that both polarities can excite the AN. Furthermore, it was shown

that the amplitudes of PS and RPS responses were similar to those produced by RPS-IPG. However, it is not clear whether PS and RPS responses were evoked by the long-low or the short-high phase. In order to test this, we compared the latency of all these responses. The comparison between peaks in Figures 7 and 8 (or PS and RPS latencies in Fig. 6) shows that EABR latencies for RPS responses were larger than for PS responses.

The fitting of an LME model showed that the latencies of the factors peak ($p < 0.001$), pulse shape

FIG. 10. Interaction between peak and polarity estimated from PS, RPS, and RPS-IPG responses. *Error bars* correspond to the highest posterior density (HPD) intervals based on the MCMC sample for a 95 % probability content of the intervals. The size of the *vertical gray lines* in the middle highlights polarity differences between peaks.

($p < 0.001$), %DR ($p = 0.011$), and polarity ($p < 0.001$) were significant. The interaction between peak and polarity ($p = 0.002$) and the interaction among %DR, peak, and polarity ($p = 0.029$) was significant too.

Figure 11 shows the estimated latencies for the different pulse shapes and peaks. Post hoc comparisons (using Bonferroni corrections) indicated that the estimated latency difference between PS and RPS stimuli ($626 \mu\text{s}$, $\text{se} = 16 \mu\text{s}$) and the difference between RPS-IPG and RPS ($570 \mu\text{s}$, $\text{se} = 17 \mu\text{s}$) was significant ($p < 0.001$) (compare PS (triangle markers) or RPS-IPG (plus markers) against RPS (square markers) latencies in Fig. 6). This latency difference between PS and RPS responses was as long as the duration of the long-low phase of these stimuli, which lasts $600 \mu\text{s}$. This demonstrates that the short-high phase is responsible for most of the AN excitation.

The difference between PS and RPS-IPG latencies ($56 \mu\text{s}$) was also significant ($p = 0.017$). This can be observed in Figure 11 and also in Figure 6, where PS latencies (triangle markers) were, in most cases, shorter than RPS-IPG latencies (plus markers). This short latency difference suggests that the long-low phase of PS or RPS pulses may either facilitate the initiation of action potentials or it may slightly change the effective excitation site. For all pulse shapes (PS, RPS, and RPS-IPG), anodic responses (PSA, RPSA, and RPSA-IPG) had shorter latencies than cathodic responses (PSC, RPSC, and RPSC-IPG; see Fig. 6).

Figure 12 shows the interaction between peak and polarity, and it can be observed that the latency difference explained by the factor polarity was larger for peak V than for peak III. The latency difference between both polarities determined for peak III ($100 \mu\text{s}$, $\text{se} = 21 \mu\text{s}$, $p < 0.001$) was smaller than the

FIG. 11. Summary of EABR latencies for PS, RPS, and RPS-IPG stimuli. Error bars correspond to the HPD intervals based on the MCMC sample for a 95 % probability content of the intervals.

FIG. 12. EABR latency interaction between polarity and peak. Error bars correspond to the HPD intervals based on the MCMC sample for a 95 % probability content of the intervals. The size of the vertical gray lines in the middle highlights polarity differences between peaks.

latency difference determined for peak V ($205 \mu\text{s}$, $\text{se} = 20 \mu\text{s}$, $p < 0.001$). The latency difference due to the factor polarity was, on average, $153 \mu\text{s}$.

The difference between peaks III and V was 1.86 ms ($\text{se} = 22 \mu\text{s}$) for the cathodic polarity and 1.76 ms ($\text{se} = 17 \mu\text{s}$) for the anodic polarity. The mean latency difference due to the factor peak was 1.81 ms .

The factor %DR had a negative slope (similarly to SYM responses) indicating that latencies tend to be shorter when increasing the stimulation amplitude. Figure 13 shows the interaction among %DR, peak, and polarity. Latency differences per polarity were higher when measured at peak V than at peak III. Polarity differences at peak V increased when the stimulation level decreased.

FIG. 13. EABR latencies as a function of the %DR. Anodic (black lines) and cathodic (solid red lines) latencies are shown for peaks III (shorter latency responses) and peak V (longer latency responses). Dotted lines correspond to the HPD intervals based on the MCMC sample for a 95 % probability content of the intervals.

Loudness balancing task

Figure 14 shows the results of the loudness balancing task. The gray diagonal serves as a reference of equal loudness. The different lines refer to the PSA (black line) and the PSC (red line) as reference stimulus, respectively. In Figure 14A, it is shown that PSC stimuli require more current than PSA stimuli to be perceived as equally loud. Note that this trend was similar either when the reference was a PSA or a PSC stimulus, though some variance was observed, especially for subject S4. This variance may be related to loudness growth and dynamic range differences between both stimuli. An increase in a fixed amount of current may produce a different increase in loudness when the polarity of the reference and the signal is swapped. The variance may also be due to possible interactions between reference and signal, where a reference of one polarity could produce more masking over a signal of opposite polarity than vice versa. Nevertheless, it can be concluded that a PSA stimulus is louder than a PSC stimulus when both are presented at the same amplitude.

The reference diagonal illustrates the hypothetical case where PSA and PSC stimuli require the same current to elicit the same loudness. Figure 14B also shows the balancing task as a function of the %DR (bottom) relative to the PSA stimulus.

In order to quantify polarity differences, linear regression lines were fitted to the normalized data by using the average data obtained from both loudness balancing measurements (PSA and PSC as references). The obtained slopes and intercepts were tested against the null hypothesis that polarity does not affect the loudness growth, i.e., a unitary slope and a zero intercept. The results for all subjects are given in Table 2.

The analysis revealed that subjects S1 and S3 both had similar intercepts for the two polarities. However, when the current amplitude increased, polarity effects were immediately observed, as revealed by the significance of their slopes.

Interestingly, for subjects S2 and S4, slope and intercept were significantly different (note that the data at lower levels do not intersect with the reference diagonal). In other words, the current needed to

FIG. 14. Loudness balancing task. **A** Loudness balancing results are illustrated as a function of the stimulus amplitude. **B** The same data are illustrated as a function of the percentage of the DR (relative to the PSA stimulus). The *black lines* correspond to the results obtained when the reference was the PSA stimulus, whereas the *red*

lines correspond to the results obtained when the reference was the PSC stimulus. *Error bars* indicate standard deviations of each condition. The *bold line* corresponds to the linear regression line. The *diagonal* serves as a reference of equal loudness.

TABLE 2

Loudness balancing analysis. Slopes (b) and intercepts (a) of the best linear fittings were obtained from the normalized loudness balancing data. Subjects, slopes (b , in %DR-PSC/%DR-PSA), intercepts (a , in %DR-PSC) together with the t values (t , with 18 degrees of freedom), and p values (p) of each parameter are also indicated in the table (significant p values are shown in bold).

Note that the null hypothesis was that polarity does not affect the loudness growth

	b	t_b	p_b	a	t_a	p_a
S1	1.5	6.3	< 0.01	5.7	1.3	0.22
S2	1.7	7.9	< 0.01	164.3	30.9	< 0.01
S3	1.6	14.4	< 0.01	-1.0	-0.4	0.72
S4	1.3	5.1	< 0.01	26.0	6.3	< 0.01

evoke the same loudness was always higher for the PSC than for the PSA stimuli. A large polarity effect was observed for subject S2, where the threshold of the PSC stimuli was higher than the CL of the PSA stimuli. This may explain, in part, the absence of EABRs for subject S2 with any of the cathodic stimuli (PSC, RPS, and RPSC-IPG).

DISCUSSION

Artifact cancellation

EABR measurements are commonly obtained by averaging responses of opposite polarity in order to cancel electrical artifacts. Electrical artifacts depend on several factors such as stimulation mode, amplitude, phase duration, and stimulating electrode. The larger the phase width or the stimulating amplitude, the larger the electrical artifact. In some cases, artifact cancellation is not necessary when SYM stimuli are used (cf. SYM responses in Fig. 4) because of relatively small electrical artifacts (Davids et al. 2008; Gordon et al. 2008), or in some cases, a simple linear regression fitting can be applied to remove the linear component of the artifacts (Brown et al. 2000; Hay-McCutcheon et al. 2002; Tavartkiladze et al. 2000). However, even with SYM stimuli (without alternating polarity), EABR artifacts can span the neural response, thereby prohibiting detection of the response or distorting it. Bahmer et al. (2010) have recorded EABRs by using SYM triphasic pulses, where the pulse shape consists of three phases (with the current of the central phase twice as high as that of the lateral phases) and precision triphasic pulses, where the ratio between the initial and last phase is adjusted to have different currents but with a total charge of zero when summing the charge of the three phases. They used precision triphasic pulses in order to minimize the electrical artifact under the assumption that this stimulus can restore the neural potential to its resting potential faster than SYM pulses. They showed that precision triphasic pulses can reduce the artifacts in comparison with SYM pulses presented at the same amplitude. However, precision triphasic stimuli elicit

lower loudness than SYM pulses. As a result precision triphasic pulses need to be presented at higher amplitudes thereby increasing the electrical artifact. The method presented in this study to cancel the electrical artifact has shown to be robust and allowed us to study responses to different pulse shapes despite the presence of huge electrical artifacts (cf. RPS-IPG stimuli in Fig. 3).

Effective phase of asymmetric pulses

As stated in the “Introduction,” all previous behavioral studies data were obtained in the presence of a counteracting phase of opposite polarity (Macherey et al. 2006, 2008, 2010, 2011). Several physiological and psychophysical studies in animals and humans have shown that the current needed to reach threshold decreases with an increase of the PW (Bonnet et al. 2012; McKay and McDermott 1999; Miller et al. 1999a; Moon et al. 1993; Pfungst et al. 1991; Prado-Guitierrez et al. 2006; Shepherd and Javel 1999; Zeng et al. 1998). It has been shown that shorter SYM stimuli are louder than longer ones when the PW is varied, but the amount of charge is kept the same (Zeng et al. 1998). However, this may not necessarily be applicable to asymmetric pulses where both phases have different amplitudes.

If the AN is more sensitive to the anodic than to the cathodic phase, then the neural response to a PSC or RPSC pulse might in principle be caused, not by the short-high cathodic phase, but by the long-low anodic phase. However, comparison between PS and RPS responses showed that EABRs were time locked to the short-high phase of asymmetric stimuli, demonstrating that this is the phase responsible for the AN excitation, irrespective of polarity. In other words, the effect of phase duration on neural sensitivity was larger than that of polarity.

Polarity and stimulation level

Concerning the polarity, results obtained in this study show that EABR amplitudes obtained with SYMA

stimuli did not differ significantly from responses obtained with SYMA stimuli. Conversely, responses to PS, RPS, and RPS-IPG stimuli showed higher responses to the anodic than to the cathodic phase, in agreement with the hypothesis that the anodic polarity is more effective than the cathodic one.

Physiological data (Ranck 1975) and computational models (Basser and Roth 2000; Frijns et al. 1996; Rattay 1986, 1999; Reilly et al. 1985) suggest that a stronger cathodic current will depolarize locally the AN fibers at the site close to the electrode, but they will become hyperpolarized on either side, i.e., more peripherally and centrally with respect to the electrode position. This means that action potentials caused by a cathodic current presented at a high level will not be able to propagate through the hyperpolarized sites ("virtual anodes"). At lower stimulation levels, the magnitude of hyperpolarization at central and peripheral sites from the stimulating electrode will decrease, and action potentials will be able to propagate through them, albeit more slowly because it will take longer to depolarize these sites. The opposite pattern is predicted for the anodic current, i.e., at high stimulation levels, action potentials will start and propagate from these lateral depolarized sites ("virtual cathodes"), whereas at low stimulation levels, depolarization will not be strong enough to initiate action potentials. The above mentioned suggests that polarity sensitivity may be level dependent, with the anodic polarity being more effective at high stimulation levels and the cathodic polarity more effective at low stimulation levels.

However, the psychophysical loudness balancing task showed that the polarity effect emerged at very low stimulation levels for all subjects. In one case, for subject S2, the threshold of the PSC stimuli was higher than the CL of the PSA stimuli. This specific case may reflect a high degree of peripheral degeneration (see "Applications").

Polarity and electrode–neuron interface

Animal and computational models suggest that polarity sensitivity depends on the electrode–neuron interface. Data by Ranck (1975) indicate that some neurons, which were stimulated with an electrode placed on the opposite side of the cell body from the axon, sometimes yielded lower thresholds for anodic than for cathodic currents. The model of an AN fiber by Rubinstein (1993) indicated that a stimulating electrode situated near the end of a fiber may result in lower cathodic than anodic thresholds, whereas a stimulating electrode situated between the end and a mid-portion of a fiber may reverse the polarity sensitivity. Furthermore, the computational model of Rattay et al. (2001) indicated that the central axon was

more sensitive to anodic than to cathodic currents. Rattay et al.'s (2001) model showed that when the electrode was close to the soma of human AN fiber with a long peripheral process (2.3 mm), the anodic current excited the central axon and had a higher threshold than the cathodic current, which excited the peripheral process. In the case of a human AN fiber with a short peripheral process (1.5 mm), Rattay et al.'s (2001) model showed similar excitation patterns, i.e., the anodic current excited the central axon and the cathodic current excited the peripheral process. However, the anodic threshold was about two times lower than the cathodic one.

From the studies mentioned above, it is possible that polarity sensitivity is not only reflecting the status of the AN nerve, but also the position of the stimulating electrode relative to the AN fibers.

Polarity and excitation site

Analyses presented in this study revealed that latencies were shorter for all anodic stimuli (SYMA, PSA, RPSA, and RPSA-IPG) than for cathodic stimuli (SYMC, PSC, RPSC, and RPSC-IPG). These differences are likely to arise from several factors: different excitation sites along the AN fibers (more central or peripheral excitation), time delays caused by the different pulse shapes, membrane properties, electrode–neuron distance, or a combination of these factors.

Since EABR amplitudes of SYMA and SYMC stimuli did not differ significantly and the anodic polarity appears more effective than the cathodic polarity, SYM latency differences indicate that the anodic phase is responsible for most of the excitation. This seems likely since the estimated latency difference between SYMA and SYMC was 80 μ s while the PW used was 75 μ s, indicating that EABRs were time locked to the anodic phase of the SYM stimulus. This conclusion is also supported by the lack of interaction between peak and polarity, which indicates that this latency difference is similar for both peak III and V, and this is also in agreement with ECAP responses recorded with SYM stimuli, where the latency difference between SYMA and SYMC responses was similar to the different PW used in the measurements (Undurraga et al. 2010).

Latency differences between anodic and cathodic responses were more complex for PS, RPS, and RPS-IPG stimuli than for SYM responses. They were larger than for SYM stimuli and were larger when measured at peak V. A possible explanation is that responses elicited by the anodic phase of the asymmetric pulse shapes are more central than those evoked by the cathodic phase. Miller et al. (1999c) showed that intracochlear stimulation with monophasic cathodic

pulses had longer latencies than anodic pulses when recorded via an electrode placed on the nerve trunk of the cat. They suggested that the anodic phase may stimulate more centrally than the cathodic phase. They also found that the cathodic phase elicited action potentials at lower stimulation levels than the anodic phase. In another study, ECAP responses recorded with an electrode in the nerve trunk had shorter latencies for anodic than cathodic pulses, suggesting central excitation by the anodic phase of a pulse (Miller et al. 2004). Latency differences found in this study are in agreement with the hypothesis of more central excitation by the anodic phase but in disagreement with the higher sensitivity to the cathodic phase found in the cat. Several studies have shown that deafened ears suffer from partial to complete degeneration of the peripheral process (Fayad and Linthicum 2006; Hinojosa and Marion 1983; McFadden et al. 2004; Nadol 1997; Nadol et al. 2001; Shepherd and Hardie 2001; Zhou et al. 1995). Rattay et al.'s (2001) model indicated that human AN fibers with degenerated peripheral processes were more sensitive to the anodic than to the cathodic polarity and that an anodic phase excited the AN fibers at the central axon. The cathodic phase initiated excitation at the soma, where the thresholds were higher than at any other site. Moreover, computational models suggest that the somatic delay is in the order of 150 to 400 μ s (Briaire and Frijns 2005; Rattay et al. 2001), which is in the order of the latency difference found here. The fact that latency differences were larger at peak V than at peak III may be due to a combination of temporal jitter and differences in temporal integration at central pathways of the auditory system as discussed below.

Polarity and synchronization

Miller et al. (1999c) showed that monophasic cathodic intracochlear stimuli elicit action potentials with longer latencies, greater jitter and relative spread than anodic stimuli. Moreover, they found that the latency was positively correlated with both jitter and relative spread of fibers.

These findings suggest that poor synchronization may occur as a result of the cathodic polarity exciting either the remaining peripheral processes or the AN somas. For AN fibers with remaining peripheral processes, the loss of synchronization may arise from length differences of peripheral fibers (Mino et al. 2004), propagation delay due to hyperpolarized sites ("virtual anodes") as well as the degree of myelination of those partially degenerated fibers that will lead to increasing time constants (Koles and Rasminsky 1972; Tasaki 1955). For AN fibers without peripheral processes, it is likely that the cathodic polarity excites

the AN's somas which differ in size across fibers and which are almost unmyelinated (surrounded by one or a few myelin lamellae) (Liberman and Oliver 1984; Rask-Andersen et al. 2000; Spoendlin and Schrott 1989). These factors can decrease the synchrony of spikes elicited by cathodic pulses significantly.

As shown in Figure 12, the latency difference measured at peak V was significantly higher than at peak III. Moreover, latency differences at peak V increased at low stimulation levels (see Fig. 13). This difference may be explained by a combined interaction between the temporal jitter and the physiological properties of neurons at higher stages of the ascending auditory pathways. The cochlear nucleus contains a diversity of cell types such as stellate, bushy, and octopus cells that project to different central nuclei including the inferior colliculus, ipsi- and contralateral superior olivary complex, and ventral nucleus of the lateral lemniscus (e.g., Joris et al. 2004). It has been shown that these different cells have different physiological properties. For example, membranes of bushy and octopus cells in mammals have a non-linear current-voltage relationship which reduces their ability to integrate temporal information (Golding et al. 1995; Wu and Oertel 1984). This allows bushy and octopus cells to preserve or enhance spike synchronization, due to the fact that they will fire preferentially when spikes are relatively coincident in time, acting as coincidence detectors (Bal and Baydas 2009; Carney 1990; Golding et al. 1995; Joris et al. 1994a, b). Conversely, stellate cell membranes have linear current-voltage relationships which allow time integration (Oertel 1983; Wu and Oertel 1984). Cells with non-linear membrane properties can be found in other stages of the ascending auditory pathways: the medial superior olive (Smith 1995), medial nucleus of the trapezoid body (Banks and Smith 1992), ventral nucleus of the lateral lemniscus (Wu 1999; Zhao and Wu 2001), and the inferior colliculus (Bal et al. 2002). Cells with linear membrane properties can be found in the ventral cochlear nucleus (Wu and Oertel 1984), medial nucleus of the trapezoid body (Banks and Smith 1992), lateral superior olive (Wu and Fu 1998), ventral nucleus of the lateral lemniscus (Wu 1999; Zhao and Wu 2001), and the inferior colliculus (Bal et al. 2002).

Given that peak III is mainly generated by the cochlear nucleus and peak V is generated by the lateral lemniscus-inferior colliculus (e.g., Legatt 2002; Møller et al. 1995), it is likely that small time differences at peak III will result more evident at higher levels of the auditory pathway (peak V) as a result of the interaction between linear and non-linear time integration along the ascending stages.

If so, lower synchronized spikes elicited by the cathodic phase (exciting more peripherally) than by

the anodic phase may produce longer latencies at peak V as a result of the above-mentioned mechanisms. Likewise, the increase in latency difference at peak V suggests that the cathodic polarity excites even more peripherally at low stimulation levels, where fibers may present a higher variance in degree of myelination and length that, consequently, can increase the temporal jitter. This idea seems to be in line with auditory brainstem recordings where longer III–V interpeak latencies were observed when the stimulation rate was increased (Debruyne 1986; Jiang et al. 1991). This agrees with increased temporal jitter at higher than at lower stimulation rates.

ECAP and EABR

Previous studies have demonstrated that human ECAP responses with asymmetric and SYM stimuli with a long IPG could be obtained when the effective phase of the stimuli was anodic (Macherey et al. 2008; Undurraga et al. 2010, 2012).

Since an electrical stimulus can depolarize AN fibers at several sites (Rattay et al. 2001), generating action potentials that travel both towards the edge of the fibers (antidromic) and towards the central auditory system (orthodromic), it has been suggested that ECAP responses may contain neural activity that travels in both directions (Briaire and Frijns 2005; Miller et al. 2004).

Miller et al. (2004) found that intracochlear ECAP responses to anodic pulses (in cats) exhibited a positive-to-negative morphology similar to the one recorded when stimulating with an electrode in the nerve trunk while recording with an electrode in the round window of guinea pigs (Brown 1994). They suggested that this morphology is due to antidromic action potentials. Similarly, the computational model of Briaire and Frijns (2005) indicated that SYMA and SYMC stimuli produced antidromic and orthodromic action potentials in AN fibers with myelinated peripheral processes. In the case of unmyelinated peripheral fibers, ECAP responses to SYMA pulses also produced antidromic and orthodromic action potentials. However, SYMC pulses produced action potentials starting at central axons that could only propagate orthodromically. In this condition, ECAP responses were very small. The response of their model to SYMC pulses showed shorter latencies than to SYMA pulses, consistent with the effectiveness of the cathodic phase. Their model suggests two things: first, ECAP responses mainly contain antidromic spikes, and second, the absence of ECAP responses to the cathodic phase may be just due to central excitation and absence of antidromic spikes.

In this study, we have demonstrated that EABRs can be obtained with both polarities with RPS-IPG

stimuli. However, the absence of ECAP responses to cathodic pulses does not seem to agree with central excitation and absence of antidromic spikes. If this was the case, we could have expected shorter EABR latencies with SYMC, PSC, RPSC, and RPSC-IPG than for stimuli of opposite polarity. Therefore, it is possible that ECAP responses are mostly showing compound action potentials that are highly synchronized in time, whereas EABR can integrate responses with larger time variability.

In a previous study, we showed that ECAP latencies and durations measured in monopolar and bipolar mode at different stimulation levels were not significantly different (Undurraga et al. 2012). This seems to indicate that ECAP responses reflect the compound activity of AN fibers that share similar anatomical properties as would be expected from central fibers.

Brown et al. (2000) found that EABR thresholds were significantly lower than ECAP thresholds, which may indeed result from higher integration time windows at more central levels. As discussed in “Polarity and synchronization,” the different nuclei along the ascending auditory pathway are able to integrate temporal information. If so, poorly synchronized cathodic responses initiated at degenerated peripheral fibers could be difficult to record by means of ECAP, the most peripheral measure, but not by means of EABR, a more central response.

Finally, though it is likely the ECAP responses contain antidromic and orthodromic spikes, the findings presented in this study correlate with previous physiological ECAP responses (higher responses to effective anodic phases) and suggest that ECAP responses to anodic pulses are composed of highly synchronized action potentials traveling orthodromically. It corroborates a previous behavioral study where place pitch differences between PSA and PSC stimuli presented in narrow BP mode were found to be dominated by the electrode at which the high-amplitude phase of a PS stimulus was anodic (Macherey et al. 2011).

Applications

EABRs to each polarity may provide the ability to assess the degree of peripheral degeneration of AN fibers. As suggested by the data, the anodic polarity seems to excite more centrally (relative to the soma of the AN fibers) while the cathodic polarity excites more peripherally. If so, the amplitude ratio between anodic and cathodic EABR may reflect the degree of peripheral neural survival. Similar amplitudes for both polarities will indicate a high degree of peripheral survival, whereas a large difference between the two will indicate poor peripheral neural survival. This idea seems to agree with our data, especially with

subject S2 for whom EABRs were only obtained with the anodic phase. Moreover, his PSC threshold was higher than the CL of the PSA stimuli, and finally, he experienced the longest duration of deafness, which may have had a significant negative impact on the survival of the peripheral processes (Sly et al. 2007).

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