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Research Paper

Facilitation and refractoriness of the electrically evoked compound action potential

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ABSTRACT

In this study we aim to resolve the contributions of facilitation and refractoriness at very short pulse intervals. Measurements of the refractory properties of the electrically evoked compound action potential (ECAP) of the auditory nerve in cochlear implant (CI) users at inter pulse intervals below 300 µs are influenced by facilitation and recovery effects. ECAPs were recorded using masker pulses with a wide range of current levels relative to the probe pulse levels, for three suprathreshold probe levels and pulse intervals from 13 to 200 µs. Evoked potentials were measured for 21 CI patients by using the masked response extraction artifact cancellation procedure.

During analysis of the measurements the stimulation current was not used as absolute value, but in relation to the patient's individual ECAP threshold. This enabled a more general approach to describe facilitation as a probe level independent effect. Maximum facilitation was found for all tested inter pulse intervals at masker levels near patient's individual ECAP threshold, independent from probe level. For short inter pulse intervals an increased N_1P_1 amplitude was measured for subthreshold masker levels down to 120 CL below patient's individual ECAP threshold in contrast to the recreated state.

ECAPs recorded with inter pulse intervals up to 200 µs are influenced by facilitation and recovery. Facilitation effects are most pronounced for masker levels at or below ECAP threshold, while recovery effects increase with higher masker levels above ECAP threshold. The local maximum of the ECAP amplitude for masker levels around ECAP threshold can be explained by the mutual influence of maximum facilitation and minimal refractoriness.

1. Introduction

Neural refractoriness of the electrically stimulated auditory nerve has been investigated in animal studies (Stypulkowski and van den Honert, 1984; Cartee et al., 2000, 2006; Miller et al., 2001; Ramekers et al., 2015), clinical studies in humans aided with cochlear implants (Gantz et al., 1994; Miller et al., 2000; Charasse et al., 2003; Battmer et al., 2004; Shpak et al., 2004; Morsnowski et al., 2006; Cohen, 2009; Botros and Psarros, 2010; Fulmer et al., 2011; Kim et al., 2011; Lee et al., 2012) and in modeling investigations (Bruce et al., 1999; Mino and Rubinstein 2006; Cartee, 2000, 2006; Goldwyn et al., 2012). These examinations are generally carried out using multi-pulse stimulation paradigms, which are typically named masker-probe or paired-pulse paradigm. The refractory period of an auditory neuron starts when an action potential has been generated. The refractory period can be split into an absolute refractory period and a relative refractory period. During the absolute refractory period the neuron is unresponsive to a probe stimulus. In humans provided with a cochlear implant this period can be estimated based on electrically evoked compound action potential (ECAP) measurements and lasts about 400 µs (Morsnowski et al., 2006; Boulet et al., 2016). The absolute refractory period is followed by the relative refractory period during which the auditory neuron regains its resting state responsiveness. At the beginning of the relative refractory period the firing probability of the neuron to a threshold stimulus starts to increase from 0 and returns to 1 at full recovery. Within the relative refractory period an above threshold stimulus is required to

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generate an action potential and firing probability to a constant stimulus increases with inter pulse interval.

In cochlear implant recipients the relative refractory period of an ECAP lasts up to about 4 ms and ECAP recovery to baseline level tends to be faster at higher stimulus intensities (Finley et al., 1997; Boulet et al., 2016). Measurement of ECAP recovery functions with paired electrical pulses revealed that neural responsiveness can be enhanced for a short period immediately following the conditioning pulse stimulus. Stypulkowski and van den Honert (1984) first noted this effect in studies of the electrically stimulated auditory nerve in cats by ECAP and electrically evoked auditory brainstem response (EABR) recordings, when the masker probe intervals (MPI) were below 300 μs. They referred to this effect as 'temporal summation' of the two stimuli which was most clearly observed at sub-maximal stimulus levels. In Guinea pigs, Miller et al. (1993) also noted related nonmonotonicities in the EABR recovery functions but not as consistently as seen by Stypulkowski and van den Honert (1984). The same effect was observed in single auditory nerve fiber recordings in cats for MPIs up to 300 μs when subthreshold and near threshold conditioning masker stimuli were used (Dynes, 1996; Cartee et al., 2000, Cartee et al., 2006). In all studies the magnitude of the temporal summation effect increased with decreasing MPIs.

The summation effect, also referred to as facilitation or integration, was also observed in clinical studies with human cochlear implant recipients using ECAP recordings (Abbas et al., 1997; Finley et al., 1997; Cohen, 2009) and EABR recordings (Hey, 2003). Temporal integration of pulses was also observed in the ECAPs evoked in cochlear implant recipients during the first two pulses of a high rate pulse train with inter pulse intervals below 500 μs (Wilson et al., 1997). Psychophysical studies with double pulses in cochlear implant recipients showed summation effects occurring at inter pulse intervals below 2 ms (Nelson and Donaldson, 2001; Karg et al., 2013). This effect was most pronounced for low level stimuli and was proposed to be related to the dynamics of the auditory neurons.

The recent review article by Boulet et al. (2016) gives an excellent overview of the temporal considerations for electrical stimulation of the auditory neuron and the mechanisms behind the effects. In this paper we will use the term facilitation in accordance with Boulet et al. (2016). The facilitation effect is thought to be caused by residual subthreshold depolarization of neurons in which the masker did not generate an action potential (Stypulkowski and van den Honert, 1984; Finley et al., 1997). This depolarization is short lasting and temporarily lowers the threshold and facilitates the probability of firing to the probe. Its dynamics has been incorporated into modeling studies (Cartee, 2000, 2006; Goldwyn et al., 2012).

Fig. 1 shows an example of a typical ECAP recovery function on a logarithmic time scale obtained in a cochlear implant patient making use of the recording method described by Miller et al. (2000). In this example facilitation responses show up at MPIs below 300 μs. Absolute refractoriness lasts up to 500 μs. Relative refractoriness starts at MPIs >500 μs and ends at about 3–4 ms. It needs to be noted that in ECAP recordings facilitation and absolute refractoriness overlap while both phenomena cannot be recorded simultaneously within a single neuron. In single neuron recordings the first pulse depolarizes the neuron towards an action potential and then the absolute refractory period starts, alternatively the neuron shows depolarization below spike threshold and then the facilitation period starts.

In this study we will focus on the stimulus-response phenomena measured at different ECAP levels for short MPIs. We anticipate that at short MPIs both facilitation and absolute refractoriness effects will affect the ECAP as it represents the synchronized excitation of multiple neurons. Some neurons will be excited by the masker and go into absolute refractoriness, while others are depolarized below the excitation threshold which will facilitate the response to the consecutive probe.

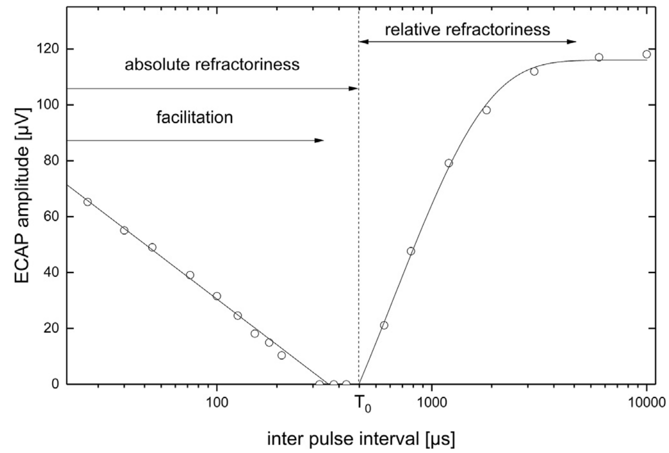

Fig. 1. Schematic drawing of N_1P_1 amplitude of a compound action potential as a function of masker probe interval. T_0 is the estimate of the absolute refractory period.

We aim to systematically investigate the refractoriness and facilitation phenomena at short MPIs by systematic variation of the masker current level (MCL), probe current level (PCL) and the MPI to further describe the ECAP behaviour in order to get a better understanding of the mechanisms behind its behaviour.

2. Materials and methods

Local ethics approval (D 469/15) was obtained before the start of the study. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee as well as with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.1. Study population

Post-lingually implanted adult CI users were recruited for this study. They were making use of a CI24RE(CA) cochlear implant or a CI512 cochlear implant (Cochlear Ltd., Sydney, Australia) on average for 26 months with a range from 1 to 101 months. Previous bilateral implantation was not an exclusion criterion and patients were measured on one side only for this investigation. All 21 patients had a full insertion of their electrode array and all electrodes were used in their everyday maps. Patient's age at investigation was on average 57 ± 20 years and ranged from 18 to 81 years. Demographics of the study population are given in Table 1.

2.2. Measurement equipment and ECAP recording parameters

All measurements were performed using the clinical Custom Sound EP v4 software (CSEP) (Patrick et al., 2006). To implement the measurement paradigms with variation of the recording parameters time-efficiently, the measurement sequences were predefined as csv files and imported into the CSEP software application controlling the actual recordings.

ECAPs were measured using the "Masked Response Extraction" paradigm (MRE) introduced by Miller et al. (2000). This method is based on two pairs with masker and probe and masker-only stimuli. With the first pair, the MPI is varied to facilitate recording of an ECAP recovery function. The second masker-probe