Effects of acoustic noise on the auditory nerve compound action potentials evoked by electric pulse trains

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Abstract

This study investigated the effects of acoustic noise on the auditory nerve compound action potentials in response to electric pulse trains. Subjects were adult guinea pigs, implanted with a minimally invasive electrode to preserve acoustic sensitivity. Electrically evoked compound action potentials (ECAP) were recorded from the auditory nerve trunk in response to electric pulse trains both during and after the presentation of acoustic white noise.

Simultaneously presented acoustic noise produced a decrease in ECAP amplitude. The effect of the acoustic masker on the electric probe was greatest at the onset of the acoustic stimulus and it was followed by a partial recovery of the ECAP amplitude. Following cessation of the acoustic noise, ECAP amplitude recovered over a period of approximately 100–200 ms.

The effects of the acoustic noise were more prominent at lower electric pulse rates (interpulse intervals of 3 ms and higher). At higher pulse rates, the ECAP adaptation to the electric pulse train alone was larger and the acoustic noise, when presented, produced little additional effect. The observed effects of noise on ECAP were the greatest at high electric stimulus levels and, for a particular electric stimulus level, at high acoustic noise levels.

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1. Introduction

Electric stimulation of the auditory nerve by a cochlear implant is the method of choice for the treatment of severe and profound hearing loss. Clinical criteria for cochlear implantation have become more relaxed over the last decade, and many patients with residual hearing have been receiving cochlear implants (NIH Consensus Statement, 1995). Studies by Turner and Gantz (2001), Turner et al. (2003) and Gstoettner et al. (2004) have demonstrated that hair cells can remain functional in patients following cochlear implantation. Therefore, there is a possibility that residual acoustic sensitivity can influence responses of the auditory nerve fibers to electric stimuli delivered by the cochlear implant. A systematic understanding of possible interactions between acoustic and electric stimuli at the level of the auditory nerve may facilitate improvements of stimulation paradigms in individuals with residual hearing.

Abbreviations: ACAP, acoustically evoked compound action potential; ECAP, electrically evoked compound action potential; IPI, interpulse interval

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1.1. Previous relevant research

Previous work in our laboratory addressed the effects of functional hair cells on the response properties of the electrically stimulated auditory nerve. It was found that presence of functional hair cells – even without acoustic stimulation – could affect the response of the auditory nerve to electric stimuli (Hu et al., 2003). Specifically, electrically evoked compound action potential (ECAP) growth functions in response to single electric pulses had smaller saturation (maximum) amplitudes and more shallow slopes in acoustically sensitive ears compared with deafened ears. In addition, it was demonstrated that viable hair cells could affect the adaptation and refractory properties of the auditory nerve, as evidenced by compound action potential recordings in response to electric pulse trains. The observed effects were attributed to increased stochastic activity of the auditory nerve fibers associated with spontaneous release of neurotransmitter by functionally active hair cells.

Preliminary studies in our laboratory have investigated effects of acoustic stimuli on the auditory nerve response to simultaneous electric stimulation. This interaction has been addressed using measures based both on ECAP (Miller et al., 2000) and single fiber (Miller et al., 2003a) responses. When presented simultaneously, wideband acoustic noise can decrease the amplitude of ECAP response to single electric pulses. Analysis of single-fiber data showed that this effect was associated with an increase of fiber discharge rate, an increase in spike jitter, a decrease in vector strength, and reductions in amplitude of individual spikes (Miller et al., 2003a). Based on these results, it was hypothesized that ECAP decrements can indicate an acoustically driven desynchronization of responses of the auditory nerve fibers to pulsatile electric stimuli.

1.2. Motivation and goals

While the aforementioned studies demonstrated acoustic–electric interactions, they provided little information about the time course of the observed effects of acoustic stimuli. As most cochlear implants present information to the auditory nerve as trains of amplitude modulated electric pulses, it is important to consider the temporal properties of acoustic–electric interaction.

Studies of electric pulse train responses in deafened animals have demonstrated that the auditory nerve response can undergo significant changes over the course of the pulse-train stimulus. Short-term adaptation to electric pulse trains that occurred over tens of milliseconds (Javel, 1990; Haenggeli et al., 1998; Matsuoka et al., 2000) as well as long-term cumulative effects that spanned over seconds (Haenggeli et al., 1998; Abkes et al., 2003) have been described. Furthermore, the magnitude and time course of adaptation to electric pulse trains can be affected by the presence of viable hair cells (Haenggeli et al., 1998; Hu et al., 2003). Response of the auditory nerve fibers to an acoustic stimulus may also undergo changes over time (Westerman and Smith, 1984).

The major goal of the present study was to provide a detailed description of the time course of changes in the auditory nerve compound action potential in response to electric pulse trains in the presence of broadband acoustic noise. Changes in ECAP amplitude observed during stimulation with acoustic noise (simultaneous effects) and following cessation of the noise stimulus (post-stimulatory effects) are described across different stimulus parameters. Level, duration and rate of stimulation may all affect response adaptation of the auditory nerve fibers to these stimuli (Haenggeli et al., 1998; Matsuoka et al., 2000). As adaptation may affect the time course of acoustic–electric interaction, we examined it by varying the levels of acoustic and electric stimuli, as well as the duration of acoustic and the rate of electric stimulation.

Portions of this study have appeared previously in abstract form (Miller et al., 2003b; Nourski et al., 2003a,b).

2. Materials and methods

2.1. Animal preparation

Twelve adult guinea pigs (weight range 450–620 g) free from middle ear infection were used in acute experimental sessions. Initial anesthesia was accomplished with a combination of ketamine (40 mg/kg), xylazine (7.5 mg/kg) and acepromazine (0.5 mg/kg), administered intramuscularly. A single dose of atropine sulphate (0.05 mg/kg) was given subcutaneously to reduce musocal secretion. After anesthesia was induced, the right external jugular vein was surgically exposed and a catheter was inserted to provide a route for hydration with Ringer’s solution. Then the animal was tracheotomized and connected to a ventilator (Harvard Apparatus model 665) with an oxygen supply (5 ml tidal volume, 50 cycles/min respiration rate). Partial pressure of expired CO₂ was monitored throughout the experiment with a capnometer (BCI model 9004) and maintained at 25–35 mm Hg. Core temperature, heart rate and blood oxygen saturation were monitored with a vital signs monitor (Pace Techn, model 4000B). Core temperature was maintained at 38 ± 1 °C with a circulating water heating pad and drapes. The effectiveness of anesthesia was assessed every 30 min using a paw pinch reflex and maintenance anesthesia (one third of the amount of initial anesthesia) was given if needed.

The animal’s head was immobilized by a custom-designed head holder. After a subcutaneous injection of
lidocaine with epinephrine (1%), an incision above and posterior to the left auricle was made and the skin flap and underlying muscles were reflected to expose the bulla. The cartilage of the left ear canal was cut to facilitate coupling with a speculum and earphone. A small defect in the lateral wall of the bulla was made with a cutting burr to expose the base of the cochlea. A cochleostomy was performed using a fine needle to access the scala tympani of the first cochlear turn. For electric stimulation, a monopolar electrode made from Teflon-insulated Pt/Ir (90%/10%) wire (with a 1 mm length stripped of its insulation) was used. This electrode was inserted through the cochleostomy into the scala tympani to a depth of about 1 mm. A return needle electrode was placed in the left forepaw.

The left parietal bone superior to the external auditory meatus was thinned with a cutting burr and removed with a rongeur to expose the flocculus. The flocculus was then retracted medially with cotton balls to provide access to the auditory nerve trunk. The ECAP was recorded using a pair of Pt/Ir (90%/10%) ball electrodes with insulated shanks. The positive-input electrode was placed about 1 mm superior to the nerve trunk, and the negative-input reference electrode was 2 mm superior to the positive input. The space around the recording electrodes was filled with saline. The ground electrode was placed in a neck muscle. Stimulation and recording were performed in a double-walled sound booth.

Surgical and experimental protocols were approved by the University of Iowa Animal Care and Use Committee and were conducted according to animal use standards of the National Institutes of Health.

2.2. Stimulus generation

Stimuli were generated by a 16-bit digital-to-analog converter at a sampling rate of 100,000 samples/s, controlled by custom-designed software written using the LABVIEW® programming environment. Acoustic clicks were generated by driving an earphone (Beyer model DT-48) with 100 µs/phase biphasic electric pulses at a repetition rate of 33 pulses per second. Bursts of broadband acoustic noise were produced by a noise generator (Grason-Stadler model 455C). The noise was gated by a Wilsonics electronic switch using a rise/fall time of 1 ms. The generator output was fed to an attenuator (Hewlett-Packard), an impedance-matching transformer, and the earphone coupled to an otoscopic speculum. In earlier experiments, sound pressure level in the ear canal was estimated using a calibration cavity which approximated the volume of the guinea pig ear canal. For later experiments, we used a probe tube and a 1/4-in. condenser microphone coupled to the speculum to calibrate the level in individual subjects.

In all cases, the acoustic noise was presented 50–100 ms after the onset of the electric pulse train. This was done to avoid the large transient effect due to short-term adaptation of the auditory nerve response to the electric pulse train. The duration of the acoustic noise burst was fixed as 300 ms in most experiments. To assess the effects of noise duration on the ECAP response to pulse trains following the offset of noise, the duration of the noise stimulus was varied from 50 to 1600 ms. The highest noise level was approximately 105 dB SPL (overall level).

Biphasic (40 µs/phase) rectangular electric pulses with alternating stimulus polarity were fed to an optically isolated, capacitively coupled current source. The output of the current source was monitored with an oscilloscope through an optically isolated path. In most experiments, the pulses were presented in 600 ms pulse trains separated by 900–1200 ms silent inter-train intervals. Inter-pulse interval (IPI), defined as the time between the onsets of adjacent pulses, was set at 4 ms in experiments assessing effects of stimulus level on acoustic–electric interactions. This rate was low enough to prevent adaptation to the electric stimulus from dominating over possible acoustic–electric interactions. On the other hand, it provided a reasonable temporal resolution to evaluate changes in ECAP throughout the duration of the pulse train. We also explored rate effects by systemically varying the IPI from 1 to 6 ms in four of our experiments. In experiments that addressed the effects of noise duration on the ECAP response to pulse trains following the offset of noise, the pulse train duration was varied from 450 to 2000 ms, with the inter-train interval set 1.5–2 times longer than the train duration. This variable silent interval was chosen to avoid significant across-train effects on the neuronal responsiveness.

For pulse-train data collection at lower pulse rates (IPI = 3 ms and greater), we used a staggered stimulus onset stimulus paradigm, illustrated in Fig. 1. This approach entailed collection of responses using three different noise onset times relative to the onset of the pulse train. In this way we could effectively examine the response to the pulse train with a three-fold increase in temporal resolution (1.33 ms, compared to the actual IPI of 4 ms in most experiments), thus improving our ability to accurately model adaptation effects. For the first pulse train, noise onset time was set to 50 ms (in two of the experiments) or 100 ms (in all other experiments). For the second and the third train, the noise onset time was shifted to an earlier time, with the difference corresponding to 1/3 and 2/3 of IPI, respectively. Additionally, every third “electric + acoustic” stimulus was followed by a control “electric only” condition (i.e., electric pulse train without simultaneous acoustic noise). The same sequence of four pulse trains was then repeated with pulse trains of the opposite polarity. Thus, a total of eight stimuli were repeatedly presented and
the response to each was averaged separately and stored to disk.

2.3. Recording techniques

Evoked potentials were amplified with a gain of 20 dB, low-pass filtered with a cutoff frequency of 20 kHz (6 pole Butterworth low-pass filter) and digitized by a 16-bit converter at a sampling rate of 50,000 samples/s for subsequent analysis. Acoustic sensitivity was assessed by measuring the acoustically evoked compound action potential (ACAP) in response to a click stimulus and determining a threshold response level. ECAP response growth functions were obtained by presenting alternating-polarity single biphasic electric pulses (40 μs per phase) at various levels. ACAP thresholds and single-pulse ECAP growth functions were obtained repeatedly throughout the course of each experiment to monitor the stability of the animal preparation.

2.4. Data analysis

Click-evoked ACAP thresholds were determined using visual criterion. The amplitudes of ECAP responses to cathodic-first biphasic single electric pulses and electric pulse trains were measured using custom-designed software written using MATLAB® programming environment. The amplitude of the ECAP was measured from the first negative peak, N₁, to the following positive peak, P₂ (Miller et al., 1998). Responses were collected at several stimulus levels to construct ECAP growth functions. To facilitate between-subject comparison, stimulus levels for electric pulse trains were chosen based on growth functions normalized to their saturation (maximum) amplitude. In most experiments, electric pulse trains were presented at current levels that produced a response corresponding to 40%, 60%, 80%, and 95% of maximum (saturation) response amplitude.

To provide a measure of the net effect of the acoustic stimulus, response amplitudes of the electric + acoustic condition were subtracted from those of the electric-only condition. This change was typically a decrement and it was plotted for each pulse in the train as a function of time after acoustic stimulus onset. Changes in ECAP amplitude following onset and offset of the acoustic stimulus were described by fitting exponential functions to the ECAP amplitude decrease data (see Section 3 for the description of the models).

3. Results

3.1. General characteristics

Fig. 2 demonstrates an example of ECAP amplitudes in response to electric pulse trains presented at a 4 ms IPI with or without simultaneous acoustic noise. In the upper panel (Fig. 2(a)), response amplitudes to individual pulses of the train are plotted as a function of time after the onset of the acoustic stimulus. Responses to the electric pulse train presented alone (filled circles) provide a control condition for evaluating effects of the acoustic noise. It can be seen that the response amplitude to the first pulse of the train is the greatest. Following the onset of the pulse train, responses to subsequent pulses in the train decrease in a monotonic fashion. This phenomenon is consistent with earlier observations (Javel, 1990; Haenggeli et al., 1998; Matsuoaka et al., 2000) and represents adaptation of the auditory nerve response to the electric stimulus.

When wideband acoustic noise is presented during stimulation of the auditory nerve with electric pulse trains (open circles in Fig. 2(a)), it results in the reduction of the ECAP response amplitudes. This interaction effect is demonstrated in Fig. 2(b), which depicts the subtraction of the “electric + acoustic” data from the “electric-only” data.

The masking effect of the acoustic stimulus on the electric probe is not constant throughout the duration of the stimulus. The decrease in ECAP amplitude is the greatest immediately following stimulus onset (labeled “onset effect” in Fig. 2) and it is then followed by a partial recovery of ECAP amplitude to an asymptotic, or steady-state, value (as shown in Fig. 2(b)). Following cessation of the acoustic noise, ECAP amplitude eventually recovers to the “electric-only” level. In some cases, there can be a residual effect of acoustic noise on the ECAP amplitude that persists over a period of 100–200 ms (see Fig. 2).
Fig. 3 presents an example of the effects of acoustic noise presented at different intensities on the ECAPs evoked by a fixed-level electric pulse train. In Fig. 4, the intensity of acoustic noise is constant, and its effect on the pulse-train ECAP is demonstrated across four levels of the electric stimulus. These examples demonstrate that the degree of interaction between the acoustic and electric stimuli depends on the intensity of both. When presented at a moderate level (65 dB SPL), acoustic noise has a relatively small effect on ECAP amplitude, and the effect increases with the intensity of the acoustic noise (Fig. 3). For a fixed level of noise, the greatest effect on ECAP amplitude can be observed at high electric stimulus levels (Fig. 4).

3.2. Onset and steady-state effects at various stimulus levels

The magnitude of the onset effect was computed as the mean difference between response amplitudes of the “electric + acoustic” and “electric only” conditions over a time window from 3 to 6 ms following the onset of the acoustic stimulus. This window was chosen to encompass the peak onset effect. The steady-state effect of noise was calculated as an average decrease in ECAP amplitude computed over a 50 ms time window beginning 50 ms prior to the time of the noise offset.

Fig. 5 summarizes these onset (Fig. 5(a)) and steady-state (Fig. 5(b)) effects for eight subjects over a range of acoustic levels and electric levels. In this figure, the level of electric stimulus is expressed as “normalized ECAP response amplitude”. On this scale, a value of one corresponds to the electric stimulus level that evoked saturated ECAP amplitude. This was done to facilitate across-subject comparisons, as it factors out differences in absolute sensitivity among the subjects. It can be observed that, in most subjects, the maximum onset and steady-state effects of acoustic noise were achieved at high acoustic noise levels and at electric stimulus levels well above threshold-level response amplitudes. In four subjects (M69, M73, M75, M87), the effect of acoustic noise on both the onset and steady-state ECAP amplitude appears to decrease as the electric stimulus level approaches saturation. In two subjects (M73, M78), a decrease in ECAP amplitude could be elicited with a moderate (65 dB SPL) level of wideband acoustic noise. It may be concluded that the amount of masking increases with acoustic and electric stimulus levels.

An alternative to examining the difference between “electric + acoustic” and “electric only” response is to compute the ratio of these two measures. The two methods (i.e., difference and ratio) can produce different results, as the same ratio can be associated with a greater absolute decrease at higher levels of the electric stimulus. To address this concern, we performed additional analysis of the onset and steady-state effects, expressing them as ratios of the experimental and control condition. This procedure revealed similar trends.
to those presented in Fig. 5. Specifically, masked ECAP amplitudes, normalized to the control electric-only condition, decreased with acoustic and electric stimulus levels, indicating a greater masking effect of acoustic noise.

Next, we sought quantitative descriptions of the time course of the partial recovery of ECAP amplitude that was observed following the onset of the acoustic stimulus (see Fig. 2(b)). We attempted to describe this recovery by fitting an exponentially decaying function to the post-onset data (plotted as difference functions, as in Fig. 2(b)). A single exponential function with three free variables (time constant, asymptote and time offset) did not produce a good fit to the data. Then we introduced a second exponential component to the equation. The shorter of the two time constants, \( s_1 \), is described as the rapid recovery component and the longer one, \( s_2 \) is referred to as the short-term component. We therefore used the following model to describe partial recovery of ECAP:

\[
A(t) = A_1 e^{-\frac{(t-t_0)}{t_1}} + A_2 e^{-\frac{(t-t_0)}{t_2}} + A_{ss},
\]

where \( A \) – decrease in ECAP amplitude; \( t \) – time after onset of the first pulse; \( A_1, A_2 \) – magnitude coefficients; \( A_{ss} \) – steady-state decrease in ECAP amplitude.

Peri-stimulatory recovery onset time, \( t_0 \), was introduced to the model to account for delays associated with generation of the neural response (particularly, sound propagation and synaptic delay at the hair cell-auditory neuron synapse). Model parameters were fit using the Marquardt–Levenberg least squared error algorithm as implemented by SigmaPlot version 7.

An example of a fit to a recovery function is shown in Fig. 6. The flat distribution of the residuals (Fig. 6, inset) demonstrates that a double exponential function provides a good fit both to the initial phase of post-onset ECAP recovery and to the later, steady-state phase. Within-subject comparisons of ECAP recovery time constants did not demonstrate any systematic dependence on either electric or acoustic stimulus level (data not shown). Analysis of individual data from eleven subjects yielded mean recovery time constants \( t_1 = 4.13 \) ms (SD = 1.87 ms) and \( t_2 = 78.9 \) ms (SD = 29.4 ms). The model requirement for two time constants suggests that two distinct mechanisms may be responsible for the decrease in ECAP amplitude observed following the onset of the noise stimulus.

3.3. Effect of pulse rate

As noted earlier, there is clearly adaptation to the electric pulse train alone as well as an effect of simulta-
neously presented acoustic noise. We attempted to minimize adaptation due to repeated electric stimulation by using an IPI of 4 ms. In this section, we examined the influence of adaptation to the electric stimulus on our measures of the acoustic–electric interactions by systematically varying the IPI of the electric pulse train. An example of data obtained from this experiment is shown in Fig. 7. It can be observed that when pulses were presented at a relatively high rate (IPI = 1 ms), ECAP amplitudes in response to the pulse train alone exhibited rapid adaptation following the onset of the pulse train (upper graph on Fig. 7(a); filled symbols). When the acoustic stimulus was turned on at 100 ms following the train onset, it produced little additional effect on the auditory nerve ECAP amplitude (upper graph on Fig. 7(b); open symbols). At lower pulse rates, acoustic noise produced greater onset and steady-state effects (Fig. 7(b)).

The pulse-rate effects are summarized in Fig. 8 for four subjects. These data again indicate that the effect of noise on ECAP amplitude is greater at lower pulse rates (i.e., at higher IPIs) (Fig. 8(a)). The effect of IPI on onset- and steady-state decrease of ECAP amplitude in presence of noise appears to saturate. Fig. 8(b) provides a comparison between the steady-state ECAP amplitudes in the “electric + acoustic” and the “electric only” condition. It can be observed that, as the rate of electric stimulation decreases, steady-state (i.e., adapted) ECAP responses increase in the “electric + acoustic” and “electric only” conditions at comparable rates. These results indicate that adaptation to the electric stimulation is one of the factors that determine the magnitude of the effect of the acoustic stimulus on ECAP amplitude.

3.4. Offset and residual effects

After the offset of the acoustic stimulus, the ECAP amplitudes to subsequent electric pulses eventually recovered to the control (“electric only”) condition levels. This post-offset ECAP recovery had a complex time course and exhibited variability among experimental
conditions and subjects. In some conditions, response amplitudes recovered almost immediately following noise offset. In some cases, this fast recovery was also associated with an overshoot effect, i.e., response amplitudes immediately following offset of the acoustic stimulus exceeded those of the “electric only” condition (see the bottom graph in Fig. 4(b)). In most other cases, a residual effect of noise was observed, in which the response amplitude decreased relative to the control condition after noise offset.

We characterized the recovery of ECAP amplitude from noise-associated masking by three components (see Fig. 2(b)). There is a fast recovery component that immediately follows noise offset, which is followed by...
a slow component that can span 100–200 ms following cessation of the acoustic stimulus. A third component tends to be a relatively small delayed enhancement of ECAP response, which occurs around 150–200 ms after noise offset. Data from subjects that exhibited such a complex recovery time course demonstrate that fast recovery was more prominent at high electric stimulus levels, whereas the slower component dominated at lower levels of electric stimulus. This is illustrated in Fig. 4(b). In that example, at high electric stimulus levels, the ECAP amplitude undergoes complete recovery with a noticeable overshoot immediately following offset of noise. As the electric level decreases, the overshoot effect disappears, and the residual effect becomes more apparent.

The complex recovery pattern observed in Figs. 2–4 suggests that there may be multiple mechanisms contributing to the ECAP adaptation and recovery. We hypothesized that, as the effect occurred after noise offset, at least part of it might be due to a cumulative process that is dependent on the duration of the acoustic masker. To address this, we conducted an experiment in which the duration of the acoustic stimulus was varied from 50 to 1600 ms. Following noise offset, a residual decrease in the ECAP amplitude was observed, consistent with our previous observations. The time course of the offset effect of acoustic noise on ECAP amplitude was analyzed similarly to that of the post-onset recovery. Specifically, this was done by fitting double exponential decay equations to the post-offset ECAP decrease data (with $A_{ss} = 0$, as the responses were assumed to eventually undergo complete recovery). In some of our observations the post-offset recovery functions appeared non-monotonic, and this method did not produce a good fit to the data. Therefore, a rising exponential component was added to the equation, which yielded the following model:

$$A(t) = A_1 e^{(-t-t_0)/\tau_1} + A_2 e^{(-t-t_0)/\tau_2} - A_3 e^{(-t-t_0)/\tau_3},$$

where $A$ – post-offset decrease in ECAP amplitude; $t$ – time after onset of the first pulse; $A_1$, $A_2$, $A_3$ – magnitudes ($A_1 > 0$, $A_2 > 0$, $A_3 > 0$); $t_0$ – post-stimulatory recovery onset time; $\tau_1$, $\tau_2$ – rapid and short-term recovery time constant, respectively (i.e., $\tau_1 < \tau_2$); $\tau_3$ – exponential rise time constant.

An example of data from such an experiment and its regression analysis are shown in Fig. 9. It can be noted that in several cases, specifically when longer noise bursts were presented, the shape of the recovery function was more complex. In these instances, the recovery is better described by a three-component exponential function with two decaying and one rising component. This complex recovery pattern suggests that there may be several factors involved in the post-stimulatory effects of acoustic noise, including a cumulative effect that is dependent upon the duration of the acoustic stimulus.
4. Discussion

4.1. Effects of acoustic noise across stimulus parameters

The results presented in this paper provide evidence that electric and acoustic stimuli, when presented simultaneously, can functionally interact at the level of the auditory nerve. Acoustic noise can produce simultaneous as well as post-stimulatory effects on the auditory nerve responses to electric pulses. The principal result of this interaction is a decrease in the ECAP response amplitude in the presence of the acoustic stimulus (wide-band noise). This is consistent with our previous preliminary findings (Miller et al., 2000, 2003a). One mechanism that may be proposed to explain this effect is that acoustically driven neural activity desynchronizes the population response of the auditory nerve. It may be hypothesized that when the acoustic stimulus is added, each electric pulse of the train would encounter a greater proportion of auditory nerve fibers that are in a state of...
absolute or relative refractoriness following acoustically evoked spikes.

The hypothesis suggests that the effect of added acoustic noise on ECAP amplitude would increase with activity in response to the acoustic noise. The amount of acoustically evoked activity could be manipulated in our experiments by changing the intensity of the acoustic stimulus. In the present study, we have demonstrated that the maximum effect of acoustic noise on ECAP amplitude is achieved at high noise intensities.

For a particular intensity of the acoustic stimulus, acoustically evoked activity in the auditory nerve decreases over time, presumably due to peripheral adaptation. We have demonstrated that the decrease in amplitude ECAP responses to an electric pulse train is not constant throughout the duration of the noise stimulus. Specifically, there was a clear onset effect, which was followed by partial recovery to a steady state. Regression analysis of the time course of the post-onset ECAP recovery revealed that it may be described as a process that has a distinct fast (rapid) and slower (short-term) component. It may be noted that these changes in ECAP amplitudes during presentation of the noise stimulus have a shape similar to that of a single-fiber post-stimulus time histogram in response to an acoustic stimulus (Kiang et al., 1965).

More detailed examination of the time course of adaptation is also consistent with a hypothesis that the effect of acoustic stimulus on ECAP amplitude increases with neural discharge rate. Westerman and Smith (1984) demonstrated that adaptation of the auditory nerve response to an acoustic tone burst could be described by
a double exponential function. In their model, the two exponential decay time constants corresponded to rapid- and short-term components of adaptation, and the asymptote reflected the steady state. The time constant of the rapid component was in the range of 1–10 ms, whereas the short-term time constant ranged between 20 and 89 ms. The two time constants of the post-onset decay in the effect of acoustic noise determined in our study are comparable with the time constants of rapid- and short-term adaptation reported by Westerman and Smith (1984). This suggests that the partial recovery of the ECAP that follows the onset of the acoustic noise burst may at least in part be attributed to adaptation of the auditory nerve response to the acoustic stimulus. The observed pattern of changes in ECAP amplitude following the onset of noise is generally consistent with this hypothesis.

There is an obvious interaction between adaptation to electric stimuli as observed in responses to the electric pulse train alone, and the effect of the acoustic noise on ECAP. Comparison across the pulse train data obtained with various IPI’s revealed that the effect of acoustic noise on ECAP response amplitudes is dependent on the rate of electric stimulation (see Figs. 7 and 8). Higher stimulation rates (IPI < 3 ms) produced relatively large decreases of the ECAP responses to individual pulses following the onset of the pulse train. This observation is consistent with the findings of Haenggeli et al. (1998) as well as an earlier study from our group (Matsuo et al., 2000). It can be attributed to refractory effects as well as short-term adaptation of the auditory nerve response to electric stimulation.

In a previous study from our group, auditory nerve fibers were described to have a mean absolute refractory period of 330 μs and a mean recovery time constant of 410 μs (Miller et al., 2001). Therefore, when the IPI is as low as 1–2 ms, it becomes comparable with the refractory period of the neuronal membrane. If masking of the ECAP by acoustic noise were mainly achieved by putting fibers in a refractory state, as we hypothesized earlier, then the noise would produce little effect on fibers that are already refractory due to relatively high-rate electric stimulation. Short-term adaptation, which is more prominent at higher stimulation rates, would also decrease the excitability of fibers and thus affect their responsiveness to the acoustic masker. This seems to be the case; as our results indicate that refractory effects and short-term adaptation to the electric stimulus dominate the time course of ECAP responses at high pulse rates (see Fig. 8(b)). Consequently, the acoustic noise, when presented simultaneously with such a pulse train, has little additional effect on ECAP response.

Post-stimulatory effects of the acoustic noise on ECAP amplitude are more complex than simultaneous effects. We observed a variety of features of ECAP recovery following the offset of the acoustic stimulus (fast recovery, overshoot, residual effect, delayed enhancement) (see Fig. 2). Fast recovery of ECAP response amplitude, which was sometimes associated with an overshoot, is consistent with the desynchronizing masking effect of the acoustic noise. Single-fiber experiments by Harris and Dallos (1979) and Westerman and Smith (1984) have demonstrated a depression of spontaneous activity in auditory nerve fibers following the offset of an acoustic stimulus. It is reasonable to expect that when the noise is turned off, cessation of acoustically driven activity and a transient decrease of spontaneous firing rate may act to increase firing synchrony. This, in turn, could produce an immediate recovery or even an enhancement in the ECAP response to electric pulses.

Another post-stimulatory phenomenon observed in our experiments is a residual effect of acoustic noise. Slow ECAP recovery cannot be explained simply by masking of ECAP due to the desynchronizing effect of ongoing acoustically driven activity. Therefore, it suggests a second mechanism by which an acoustic stimulus may affect responses to electric stimulation. This mechanism is likely to involve adaptation of the auditory nerve fibers to acoustic stimulation, especially as the complexity of the post-offset ECAP recovery seems to increase with the duration of the acoustic stimulus (see Fig. 9). It may be hypothesized that following the cessation of the acoustic stimulus, response to electric stimuli is no longer masked by response to noise, but there is a decrease in excitability of nerve fibers due to adaptation. Consequently, they are not as responsive to electric stimulation. The residual effect of acoustic noise may therefore be attributed to recovery of ECAP from this neural adaptation.

Non-monotonic time course of the ECAP recovery functions, particularly following longer durations of the acoustic masker (see bottom graphs in Fig. 9), is comparable with recovery of ECAP response from an electric masker stimulus reported by Killian et al. (1994). The origin of this non-monotonicity is unknown. However, it may be suggested that it could result from a combination of the two mechanisms (transient decrease in spontaneous activity and recovery from adaptation in the nerve fibers).

4.2. Clinical relevance and future directions

The acoustic–electric interactions that we have observed in the present study may occur in cochlear implant patients with residual acoustic hearing. Such interactions are likely to be limited to the auditory nerve fibers that respond to both acoustic and electric stimulation. An important difference between experimental animal preparations and human cochlear implant patients is that, in the former cases, fibers can respond to both types of stimuli, whereas in the latter case there is likely
to be a spatial segregation of fibers that are responsive to acoustic and electric stimuli. Thus, such interactions might not be a concern in patients implanted with short electrode arrays, as this method implies this kind of stimulus segregation. However, the described acoustic–electric interactions may exist in cases where a broad electric field is generated by a stimulus electrode (particularly, in a monopolar mode of stimulation). In these cases, understanding of physiological phenomena associated with simultaneous acoustic and electric stimulation may be helpful for improved processing of both electric and acoustic stimuli delivered to such patients.

Future studies of effects of combined acoustic and electric stimulation on the level of the auditory nerve should address several issues. First, as adaptation to electric stimulation has been shown to affect acoustic–electric interactions, it is reasonable to evaluate these interactions in a condition free from electric stimulus-induced adaptation. That is, a forward-masking paradigm (using single electric pulses as a probe and broadband acoustic noise as a masker) may be utilized to address the interaction and, specifically, post-stimulatory effects of acoustic stimulation on ECAP.

Understanding of the observed phenomena may be facilitated by descriptions of auditory nerve fiber response properties, such as spike rate, dynamic range, jitter, and synchronization index, in combined electric–acoustic stimulation. These properties cannot be directly assessed by ECAP measures, and, therefore single-fiber studies of electric–acoustic interactions should be conducted.

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References


