

Matching the Neural Adaptation in the Rat Ventral Cochlear Nucleus Produced by Artificial (Electric) and Acoustic Stimulation of the Cochlea

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Abstract

To investigate neural adaptive properties, near-field evoked potentials were recorded from a chronically implanted electrode in the ventral cochlear nucleus in awake Long Evans rats exposed to acoustic stimuli or receiving intracochlear electric stimulation. Stimuli were 250 ms trains of repetitive acoustic clicks (10, 30 and 50 dB SPL) or biphasic electric pulses (30, 50 and 70 μ A) with intra-train pulse rates ranging from 100 to 1000 pulses per second (pps). The amplitude of the first negative (N_1) -positive (P_1) component of the average evoked potentials was measured for each consecutive individual pulse in the train. While a progressive exponential decrease in N_1 - P_1 amplitude was observed as a function of the position of the pulse within the train for both types of stimulation, the decrement of electric responses (adaptive pattern) was substantially less prominent than that observed for acoustic stimuli. Based on this difference, the present work was extended by modifying electric stimuli in order to try to restore normal adaptation phenomena. The results suggest the feasibility of mimicking acoustic adaptation by stimulation with exponentially decreasing electric pulse trains, which may be clinically applicable in the auditory implant field.

Key Words

Click · Cochlear implant · Cochlear nucleus · Latency · Near-field potential · Repetitive pulses

Introduction

As a result of sustained efforts made over the past 30 years to define features of speech coding for cochlear prostheses, many profoundly deaf patients demonstrate nowadays very high levels of speech intelligibility in quiet with their cochlear implant [e.g. Tyler et al., 1995]. However, most of the patients still complain about unsatisfactory performance in background noise [e.g. Fetterman and Domico, 2002]. Among several reasons for this, one major cause is a deterioration of the ability to process dynamic aspects of speech such as abrupt changes in intensity, spectral transitions (vowel-consonant) and different spectral components. Indeed, although the most basic characteristics of the normal auditory system such as frequency selectivity and tonotopy [Parkins and Anderson, 1983], non-linear compression and temporal coding [Wilson, 1991] are well reproduced by accurate temporal and spatial delivery of electric stimuli to the cochlea, several natural features are still not reproduced by present electric stimulation paradigms. The features not yet taken into consideration include, for instance, differences between auditory nerve (AN) fibers subpopulations in terms of spontaneous firing rates, a property correlated with threshold [Lieberman, 1978], or the decline in AN fibers' discharge rate following the onset of a tone burst referred to as a phenomenon of adaptation. Adaptation has been observed, in normal hearing conditions, at several levels of the auditory pathway. First, at the hair cell level, during translation of the stimulus into hair bundle deflection and then in the transduction of the bundle deflection into a receptor potential [data from the frog reviewed in Eatock, 2000]. Second, at the hair cell-AN fiber synapse, during transmitter release and postsynaptically [Furukawa and Matsuura, 1978]. Third, more centrally, in the population of primary auditory neurons [Eggermont and Spoor, 1973; Westerman and Smith 1984; Yates et al, 1985; Rhode and Smith, 1985; Müller and Robertson, 1991;

Javel, 1996] and in the cochlear nucleus (CN) [Møller, 1969; Evans, 1975; Huang, 1981; Burkard and Palmer, 1997; Loquet and Rouiller, 2002]. Based on numerous studies, authors seem now to agree in locating the major source of auditory adaptation at the hair cell-AN synapse, due to a depletion of available synaptic vesicles [Furukawa and Matsuura, 1978; Furukawa et al., 1982]. Adaptation observed more centrally probably reflects a combination of the adaptation taking place in the organ of Corti as well as in the central nervous system and one could argue that it is a signaling cascade in which peripheral sites reverberate their effects more centrally. This view is supported by data [Gerken, 1979] demonstrating that auditory peripheral damages affect responses evoked by central electric stimulation. In practice, in response to a tone-burst (typically 50 ms duration), but also to short repetitive tone-bursts [Müller and Robertson, 1991] or click trains [Wickesberg and Stevens, 1998], AN fibers and CN units (primary-like and chopper response types) exhibit an abrupt increase of firing rate at stimulus onset followed by a rapid decrease during the next 10-30 ms to reach a plateau maintained until stimulus offset. We may postulate that such an adaptive response pattern is likely to prevent auditory neurons from constantly discharging (in some cases at saturation) along the entire stimulus duration, in order to make them quickly sensitive again to a subsequent stimulus occurring during the ongoing initial stimulus or to a rapid change of the latter. Adaptation might therefore emphasize the contrast between novel stimuli relative to background stimuli and thus significantly contribute to improve speech perception.

However, adaptation phenomena observed during acoustic stimulation of a normal ear clearly differ from those elicited by current electric stimulation devices which still code a tone burst of constant amplitude as a current burst of constant amplitude. For example, previous studies in human subjects [Wilson et al., 1997] and in animals [Kiang and Moxon, 1972; Hartmann et al., 1984; Van

den Honert and Stypulkowski, 1984; 1987; Javel et al., 1987; Parkins, 1989; Haenggeli et al., 1998; Matsuoka et al., 2000] have established that evoked potentials or discharges of AN fibers in response to electric stimuli are excitatory responses, precisely phase-locked to sinusoidal or pulse-train stimuli for low stimulation rates (<1 kHz or 100-200 pulses per second). Furthermore, increasing stimulus intensity produced a greater degree of synchronization but no adaptation. In contrast, for higher rates, an adaptation effect has been reported in the AN in both humans [Wilson et al., 1997] and animals [Javel et al., 1987; Van den Honert and Stypulkowski, 1987; Haenggeli et al., 1998; Matsuoka et al., 2000], where the response was maximal at the beginning of a pulse-train, followed by a progressive decay to reach a plateau after 30-40 ms from stimulus onset. However, if the interpulse interval of the electric pulse train is within the relative refractory period of the stimulated fibers, then the response to the second pulse in the train is reduced and a pattern of amplitude alternation or oscillation to successive pulses was observed [Wilson et al., 1997; Matsuoka et al., 2000]. This phenomenon was more pronounced in humans than in animals and made adaptation difficult to estimate. At very high rates of pulsatile electric stimulation (4000 pps and above), due to a rapid adaptation, the response reached a plateau quickly during the first milliseconds of stimulation. Based on these data, it was suggested that speech perception could be enhanced by using such high stimulation rates in cochlear prosthesis [Wilson, 1997]. In summary, adaptation in the AN appears strongly dependent on the rate of pulsating electric stimuli, although some studies revealed a considerable inter-fiber variability in the time course of adaptation [Dynes and Delgutte, 1992; Killian et al., 1994; Litvak et al., 2001].

In the CN, adaptation phenomena [Møller, 1969; Evans, 1975; Huang and Buchwald, 1980; Huang, 1981; Boettcher et al., 1990; Shore, 1995; Burkard and Palmer, 1997; Loquet and Rouiller, 2002; Loquet et al., 2003] are more difficult

to study than in AN because of the presence of a large variety of cell types [Osen, 1969] processing in parallel the stereotyped incoming acoustic information. In the past, numerous studies have described in detail the variability of discharge patterns across CN neurons when stimulated with tones [e.g. Kiang et al., 1965; Pfeiffer, 1966; Evans and Nelson, 1973; Godfrey et al., 1975], but there have been fewer studies aimed at investigating the effects of repetitive electric stimulation of the cochlea in the different subregions of the CN [Shofner and Young, 1985; Glass, 1985; Maffi et al., 1988; Wiler et al., 1989; O'Leary et al., 1995a; Paolini and Clark, 1998; Babalian et al., 2003]. In the ventral part of the CN (VCN), pulsatile electric stimulation of the cochlea lead to a reduction of the diversity of discharge patterns as compared to acoustic stimulation. A high degree of synchronization in response to continuous constant-current sinusoids [Glass, 1984; Clopton and Glass, 1984] or to pulse-trains [Maffi et al., 1988] was observed for frequencies up to at least 12 kHz or for rates up to 800 pulses per second, respectively. In response to electric AN stimulation, intracellular recordings [Babalian et al., 2003] demonstrated that VCN cells followed with high probability each pulse in a train at low stimulation rates (200-300 pps) whereas at high stimulation rates (500-1000 pps), the usual response patterns (primary-like, onset) were evoked. In the dorsal part of the CN (DCN), neurons exhibited primary-like, onset, buildup and pauser response patterns, but none synchronized its activity to repetitive pulses even at low rates, as demonstrated on the basis of extracellular [O'Leary et al., 1994; 1995a; 1995b] and intracellular [Babalian et al. 2003] recordings.

To study neural adaptive properties further, a way could be to stimulate the same ear with both acoustic and electric stimuli in order to perform a direct comparison between the two modes of stimulation. Such an approach has been used in few studies, based on acute AN evoked compound action potential [Prijs, 1975; Simmons and Glatke, 1972; Prijs and Eggermont, 1980] or single

unit recordings [Parkins, 1989]. In the present study, we used pulsatile acoustic and electric stimuli of varying intensities and repetition rates and recorded near-field evoked potentials from a chronic electrode implanted in the VCN. This approach was chosen in order 1) to obtain stable recordings along repeated (acoustic then electric) stimulation sessions in unanesthetized adult rats; 2) to perform measures from the same ear before and after cochlear implantation allowing then direct comparisons between acoustic and electric data. First, the present study confirmed that neural adaptation to repetitive electric pulses is much less prominent than in response to acoustic repetitive pulses. Second, the comparison of acoustic and electric CN evoked potentials allowed us to better infer the location of this adaptation. Finally, a paradigm of electric stimulation of the cochlea was developed yielding a neural adaptation in VCN mimicking that observed with acoustic stimulation.

Methods

Animal preparation

Male adult Long-Evans rats (Janvier Laboratories, France) weighing approximately 300 g at the beginning of the experiment underwent two surgeries at one month interval in order to record near-field potentials in the CN in response to successive stimulation of the same ear with acoustic and electric pulses. Surgical and experimental procedures were approved by the Swiss veterinary authorities and were conducted in accordance with the guidelines of the US NIH and the Declaration of Helsinki for animal care.

The first surgery, aimed to implant a chronic recording electrode in the left VCN, was described in detail in a previous report [Loquet and Rouiller,

2002] and is only briefly summarized here. Firstly, rats (n=4) were deeply anesthetized with pentobarbital (Vetanarcol®, 40 mg/kg, i.p.) and treated with Atropine sulfate (0.05 mg/kg, s.c.) to minimize respiratory distress and Carprofen (4 mg/kg, s.c.) to reduce pain. Then, they were placed in a stereotaxic apparatus and one tungsten electrode (2-4 MΩ impedance) was chronically implanted in the left VCN whereas a second electrode was inserted in the rostral cranium to serve as the ground electrode. The two electrodes were soldered to a socket, then fixed to the skull with dental cement and finally the animals were allowed to recover for one week before sessions of chronic recording in response to acoustic stimuli took place.

About one month later, the second surgery was conducted in the same rats in order to implant a chronic stimulating electrode in their left cochlea. To achieve this purpose, the animals were anesthetized (Vetanarcol®, 40 mg/kg, i.p.), treated with Atropine sulfate and Carprofen and then placed in a custom-made surgical table. A heating pad was used to maintain the body temperature within a range of 37-39°C. Through a retroauricular approach on the left side without damaging the facial nerve, the otic capsule was opened to expose the round window and, under visual control with an operating microscope, an intracochlear stimulating electrode was inserted 4 mm inside the round window (approximately half of the basilar membrane length). The electrode was a 100 μm diameter platinum-iridium Teflon® coated wire, flamed to a ball at the tip (approximately 0.15 mm) and 200 kΩ impedance (tested in saline with a 1 kHz sine wave). The electrode was then secured with connective tissue and the bulla was closed with dental cement. For the return (monopolar stimulation), a PtIr-ball electrode (ball diameter: ±0.5 mm, 100 kΩ impedance) was inserted and ligated in the *muscle cleidomastoidus*. Then, the two electrodes were soldered to the skull socket and fixed with dental cement. The electric stimulation sessions began the next day and lasted up to four days postimplantation.

Stimulation

Acoustic stimuli were generated with a Tucker-Davis Technologies system II equipment (SigGen32 software, programmable attenuator and D/A converter) and delivered via a speaker (JBL®, 2405H) positioned 10 cm away from the left pinna of the rat. Stimuli consisted of 250 ms trains of rectangular condensation clicks (100 μ s) followed by a 250 ms pause before the next train. For such a duration (100 μ s), the click has a frequency spectrum ranging from 0.25 to 10 kHz, tonotopically corresponding to about 40 % of the basilar membrane length from apex (~3.2 mm, according to Greenwood [1996]). The intra-train pulse rates varied from 100 to 1000 pulses per second (pps) and three intensities were tested: 50, 30 and 10 dB SPL. The system was calibrated with a Bruel and Kjaer 12.7 mm microphone by measuring the sound pressure level (RMS, re: 20 μ Pa) emitted by the speaker when it was driven by a train of clicks at repetition rate of 1000 pps. The calibration microphone was positioned at the location occupied by the central point of the animal's head.

Electric stimuli were generated by a programmable numerical speech processor referred to as "Geneva Wearable Processor" [Pelizzone et al., 1999] and developed by the Cochlear Implants Center at the Geneva Cantonal University Hospital. The system was built by using a Motorola Application Development System (ADS) which consists of an application development module (ADM) containing a 40-MHz Motorola 56002 DSP (Digital Signal Processor) and a software controlling the ADM. An interactive MATLAB subroutine was added to allow the user to set the characteristics of the electric stimuli (intensity, pulse rate, train duration). At the output of the system, numerical signals were converted (D/A at 20 kHz, 12 bits) into trains of biphasic pulses routed to custom optoisolated current generators and delivered directly to

the implanted electrodes in the cochlea. Single anodic-first biphasic pulses (50 $\mu\text{s}/\text{phase}$), identical to those used in human cochlear implants [Pelizzone et al., 1999], were first produced at increasing intensity levels (0 to 100 μA in steps of 10 μA) in order to establish the growth function of electric CN evoked potentials. Based on the monotonic functions obtained, three intensities were chosen, namely 30 μA (close to threshold intensity), 50 μA (intensity giving about 50% of the maximal response) and 70 μA (close to the intensity of saturation). Adaptation was tested in a way similar to acoustic stimulation and therefore the electric stimuli consisted in pulse trains of 250 ms followed by a 250 ms pause before the next train with intra-train pulse rates varying from 100 to 1000 pps. The in-situ monopolar impedance values of the intracochlear electrode ranged from 6 to 17 $\text{k}\Omega$.

Recording

Recordings were performed in an audiometric room (IAC, Germany) on awake rats placed in a restraining device [Loquet and Rouiller, 2002]. The acoustic and electric CN evoked potentials (aCNP and eCNP respectively) were amplified (2×10^3), bandpass filtered between 30 Hz and 5 kHz then fed into an A/D converter (Tucker-Davis Technologies System II). The data acquisition software BioSig32 was used to automate CNP averaging over 50 presentations, for off-line analysis, and also to trigger the electric stimulation (56002 DSP). The analysis window stretched over 250 ms. CNP latencies were measured from stimulus onset to the peaks N_1 and N_2 of the response, whereas CNP amplitude was measured as the voltage difference between the first negative (N_1) and the first positive (P_1) peaks. Because responses to individual clicks overlapped at repetition rates higher than 400 pps, CNP responses were derived using a subtraction method (fig. 1). The method consists of deriving the response to the

Nth click in a train by subtracting a record which had one less click in its train. The resulting waveform thus exhibited the CNP to the Nth click without contamination by the CNP of the preceding clicks. This method was used by other authors [Wilson et al., 1997; Rubinstein et al., 1999] and was previously validated with acoustic stimulation [Loquet and Rouiller, 2002]. The subtraction method was applied to all repetition rates tested and the N_1 - P_1 amplitude was normalized relative to either the largest CNP observed in the same train (usually the CNP to the first pulse) or to the largest CNP obtained at the highest stimulus level for a given repetition rate. The normalized CNP was then plotted as a function of the position of the corresponding stimulating pulse in the train expressed in ms from stimulus onset.

Histology

The location of the recording electrode in the VCN was verified at the end of the experiment (three months after the implantation) in all implanted rats. To achieve this purpose, the animals were deeply anaesthetized with an overdose of pentobarbital (Vetanarcol®, 80 mg/kg, i.p.) and a continuous, positive current (10 μ A) was passed through the recording electrode for 10 min. The rats were then perfused through the heart with normal saline followed by a 4% paraformaldehyde solution in phosphate buffer (0.1 M at pH=7.4). After decapitation, the brain was removed, postfixed one night in the fixative solution and kept the next day in a 30% sucrose solution at +4°C for cryoprotection. Frozen coronal sections (50 μ m thick) were cut, washed in phosphate buffer and mounted on slides. Finally, sections were counterstained with cresyl violet (Fluka, 0.06%), coverslipped with Eukitt and observed in light microscopy.

Results

The photomicrographs presented in figure 2 show the location of the tip of the chronic recording electrode used to derive CNP from VCN for two animals. A variation of insertion depth was observed but did not exceed 300 μm across animals. In all four animals, the electrode was located in the VCN.

CNP in response to steady acoustic or electric pulse trains

Examples of typical acoustic and electric CNP responses derived from the same chronic VCN recording electrode are presented in figure 3A and 3B, respectively, for the first 35 ms of 250-ms records. Very stable aCNP responses were observed over several weeks whereas the thresholds of the eCNP increased slightly starting at 5 days postimplantation. The response to individual 100 μs rectangular acoustic clicks was characterized by two negative deflections of comparable magnitude referred to as N_1 and N_2 , separated by a peak of opposite polarity (P_1). At the rate of 100 pps, aCNP magnitudes were uniform along the train for low stimulation intensities (10 dB SPL). In contrast, increasing the intensity of stimulation (30 and 50 dB SPL) resulted in an increase of the trough-to-peak N_1 - P_1 amplitude in response to the first individual click and a progressive decrease of the amplitude of the responses to the following clicks in the train. Such decrease of the response amplitude to subsequent pulses in the train reflects the phenomenon of adaptation. The aCNP latencies determined for the peaks N_1 and N_2 are presented in figure 4A and exhibited a concurrent decrease (constant interwave latencies) as a function of intensity from 10 dB SPL to 50 dB SPL. Similar to the records obtained with acoustic stimuli, the responses to individual electric biphasic square pulses (fig. 3B) exhibited successive negative peaks (N_1 and N_2), separated by a peak of opposite polarity

(P₁). In contrast, the recordings showed large residual artifacts (at most 5 times of the N₁-P₁ height) 300 μs after the onset of the stimulus and a substantially smaller N₂ peak than N₁. At the rate of 100 pps (fig. 3B), eCNP magnitudes varied largely as a function of stimulation intensity but remained remarkably constant along the train irrespective of the stimulation intensity tested (30, 50 or 70 μA). Thus, in contrast to acoustic clicks (fig. 3A), repetitive electric pulses delivered at low rates (100 pps) did not result in a significant adaptation of the response (fig. 3B). The eCNP latencies determined for the peaks N₁ and N₂ are presented in figure 4B and appeared to be independent of the intensity.

The effect of stimulation rate and intensity is illustrated quantitatively in figure 5 where amplitudes of individual CNP's to consecutive clicks (in the left column) or electric pulses (in the right column) were plotted for one representative animal. Generally, the evoked CNP showed a progressive decrease (adaptation) of the normalized amplitudes as a function of the position of the pulse along the train. On one hand, the adaptive pattern of acoustic responses is a decay which became more pronounced for increasing rates and when stimulation intensity was increased. Similarly to our previous results [Loquet and Rouiller, 2002], we found that each adaptive curve was best described by a two time constants exponential decreasing equation $y(t) = y_1 e^{-t/\kappa_1} + y_2 e^{-t/\kappa_2} + \text{Plateau}$ where y_1 , y_2 are the y intercepts of the rapid and short-term adaptive components respectively; κ_1 and κ_2 their corresponding decay time constants; and Plateau equals the N₁-P₁ amplitudes during the steady state response (results were obtained with GraphPad Prism® 3.02 software but are not shown in the present report). The adaptive pattern of electric responses was different (fig. 5, right panels). There was very little adaptation at low rates (100 and 200 pps) whereas at 400 pps and above, the decrement of amplitude became progressively greater, but still less pronounced than that observed for acoustic stimuli. The electric adaptive curves exhibited an initial rapid phase

followed by a slower phase, without plateau. This pattern was hardly or not at all influenced by the intensity of stimulation (fig. 6), whereas individual eCNP magnitudes were largely dependent on the intensity of stimulation (fig. 5, right panels). In addition, one can note that during the first 20 ms of the train, where CNP were collected for all consecutive clicks or pulses, the N₁-P₁ amplitudes of both aCNP and eCNP showed a sequential up and down alternating sequence, corresponding to an oscillation of the CNP amplitude along the train. This alternation or oscillation phenomenon was most pronounced at repetition rates of 400 pps and above, when electric stimuli were used. In contrast, oscillations were less prominent when using acoustic stimuli and only observed at high stimulation rates (fig. 7).

CNP to modified electric pulse trains

Since VCN adaptive curves in response to steady electric pulse trains were very different from those obtained with click trains (fig. 5), our goal was to adjust the parameters of electric stimulation in order to restore natural adaptation phenomena. Therefore, acoustic adaptation was tentatively mimicked by building modified electric pulse trains from acoustic adaptive curves (fig. 8). To achieve this purpose, acoustic data were reported on an electric growth function (established for each rat) in order to determine the electric stimulus intensity required to elicit a similar CNP amplitude. The resulting transformed intensity values were then plotted as a function of its position in the 250 ms train and the curve was fitted using the equation $y(t) = y_1e^{-t/k_1} + y_2e^{-t/k_2} + \text{Plateau}$. As previously, the curve fitting was obtained using the Levenberg-Marquardt method with GraphPad Prism® 3.02 software and the deviation from model was assessed by considering the correlation coefficient ($R^2 \geq 0.70$) and by testing the Gaussian distribution of the residuals around the curve ($P > 0.1$). The five

parameters (y_1 , y_2 , K_1 , K_2 and Plateau) were extracted and fed into an interactive MATLAB subroutine to produce the 250 ms exponentially decreasing electrical stimuli. In this way, new electrical adaptive patterns were obtained with the modified train of pulses (fig. 9). These data (blue curves) were obtained before the 5th postimplantation day and showed exponential decays more comparable to those obtained with click trains (red curves), namely a three-phased adaptation exhibiting an initial rapid phase followed by a slower phase and a plateau. Concurrently, the exponential decrease became more pronounced for increasing rates. In contrast, the pattern of the curve obtained with steady electric pulse trains (black curves) appeared different for rates of 200 pps to 1000 pps. Such curves (fig. 9) were compared statistically for the four rats using a two-way analysis of variance (ANOVA) performed by GraphPad Prism® 3.02 software. The results are summarized in table 1. It can be concluded that the two curves in figure 9 obtained with constant amplitude acoustic (red) and electric (black) pulse trains are significantly different, reflecting a clearly less dramatic adaptation for steady electric stimulation. In contrast, the blue curves obtained in figure 9 with modified electric pulse amplitudes were not significantly different from the corresponding acoustic curves (red) at rates ranging from 200 to 1000 pps. These data thus support the notion that the proposed modification of the electric pulse trains was successful in mimicking the natural adaptation pattern. Moreover, a further consequence of the modified electric pulse train towards a better replication of the acoustic adaptive pattern was to reduce the occurrence and amplitude of alternating patterns.

Discussion

Origin of the compound action potentials

Although the results of the present study are based on CNPs obtained from recording electrodes located in the VCN, the nature of the neural populations generating these potentials is a matter of debate. At first glance it seems reasonable to hypothesize that these responses most likely reflect the behavior of VCN neurons plus possible contributions from neurons of DCN, as well as ascending branches of incoming AN fibers. One could argue that, when advancing the electrode on a dorsal-to-ventral path through the VCN, AN fibers tend to be encountered at greater depths (i.e. more ventrally) than VCN units [Paolini et al., 2001]. However, in vivo, a determination of the recording location can be inferred only by advancing the electrode through the CN and by checking for a match with the known orderly tonotopic organization of the CN. Unfortunately, such an approach was not performed during the implantation of the recording electrode (the optimal location was assessed by only identifying the two N_1 and N_2 deflections), and therefore one cannot elaborate further on the precise neural origin of the responses. The response latencies may also provide a basis useful to infer the neural origin of the responses, by comparing them to values drawn from previous reports conducted in the rat. For example, the latency values obtained by FitzGerald et al. [2001] in the response of single units to 90 dB SPL clicks ranged from 1.5 to 3 ms in the AN (depending on their characteristic frequency) and from 2 to 4 ms in the VCN. Latency values obtained by Paolini et al. [2001] for single units in response to 100 dB SPL clicks ranged from 1.4 to 2.7 ms in the AN and from 1.8 to 4 ms in the VCN. Using tone bursts and recording intra-axonally from the ventral acoustic stria, Friauf and Ostwald [1988] obtained latencies ranging from 2.2 to 2.6 ms for identified VCN neurons. When comparing these data to our results (acoustic latency values: $1.48 \text{ ms} < N_1 < 1.76 \text{ ms}$ and $2.21 \text{ ms} < N_2 < 2.49 \text{ ms}$, depending on stimulus intensity), it is tempting to conclude, in line with Møller's data [1983],

that N_1 mainly reflects the activity in the AN whereas N_2 is predominantly generated by CN neurons, mainly VCN. Indeed, a contribution of units located in the DCN is less likely because of their low ability to follow repetitive stimulation [Rhode and Smith, 1986]. However, the interpretation of origin of the N_1 and N_2 waves is most likely not so schematic [Sellick et al., 2003]. Indeed, one may doubt that a single wave is generated by only one cell population. It is more realistic to consider the N_1 - P_1 - N_2 components as a continuum of activity reflecting a sum of superimposed activities generated by multiple neural subpopulations, both in the AN and CN.

Comparison of acoustical and electrical compound action potentials

Comparing the waveform of the acoustic and electric CNPs, it appears that they both exhibit two negative peaks N_1 - N_2 (fig. 3), with a comparable interwave latency (fig. 4). This is in agreement with previous animal and human data [van den Honert and Stypulkowski, 1986; Pelizzone et al., 1989], suggesting that the aCNPs and eCNPs were produced by similar underlying events in the auditory periphery and brainstem nuclei. However, as previously established by others [Prijs, 1975], acoustic and electric responses differ not only by their latencies but also by their detailed waveform pattern, especially when comparing N_1 and N_2 magnitudes (figs. 3 and 4). In our experiments, the recording electrode was the same for both conditions and, therefore, the reason for such differences more likely lies in the stimulation techniques used. Nevertheless, the region of the cochlea driven by acoustic and electric stimuli is probably irrelevant. Indeed, when considering first the 100 μ s acoustic click characterized by a frequency spectrum limited to below 10 kHz [Burkard, 1984], it follows that the acoustic stimulation influenced mainly the upper 40% of the rat's cochlear partition (~ 3.2 mm from apex), where are represented the

frequencies ranging from 0.25 to 10 kHz, according to Greenwood [1996]. The electric stimulation was delivered via an electrode inserted on a distance of 4 mm from the round window and thus the ball at the tip was located at the middle of the basilar membrane (~4.0 mm). The stimulus current is likely to spread as much towards the base than towards the apex of the cochlea because the ground electrode was placed far from the active electrode. It can be concluded that both modes of stimulation influenced overlapping regions of the cochlea, in particular within the 1-8 kHz frequency range, which is a domain of good hearing sensitivity in the rat [Heffner et al., 1994]. A more likely interpretation for the differences observed between acoustic and electric responses is the absence of travelling wave and transduction apparatus in the cochlea as a result of insertion of the stimulating electrode. Indeed, this interpretation is supported by an observation that an acoustic stimulation delivered after cochlear implantation failed to induce any aCNP response in the VCN (personal unpublished data). Although the extent of the damage to the cochlea due to electrode insertion is not known (histology of the cochleas was not performed), we assume, in line with previous data [Kiang and Moxon, 1972], that the electric stimulation directly affects the primary auditory neurons, thus bypassing the transduction elements, resulting in a shorter eCNP latency ($0.95 \text{ ms} < N_1 < 0.96 \text{ ms}$ and $1.52 \text{ ms} < N_2 < 1.63 \text{ ms}$, depending on stimulus intensity) than aCNP latency ($1.48 \text{ ms} < N_1 < 1.76 \text{ ms}$ and $2.21 \text{ ms} < N_2 < 2.49 \text{ ms}$). Concerning the magnitude of N_1 in comparison to that of N_2 (fig. 3), the larger N_1 wave observed in response to electric than acoustic stimuli may result from the stronger synchronized activities of auditory nerve fibers elicited by electric pulses than by clicks [Hartmann et al., 1984].

Comparison of acoustical and electrical adaptation

Increasing stimulus intensity induced, as expected [Møller, 1975; FitzGerald et al., 2001], a decrease of aCNP latencies (less marked in eCNP, fig. 4) and an increase of the N_1 - P_1 amplitude in response to the first pulse in the train (fig. 3), due to AN fiber recruitment. However, responses to the following pulses in the train varied significantly for acoustic versus electric stimulation (figs. 3 and 5). In response to trains of clicks at repetition rates ranging from 100 to 1000 pps, CNPs were synchronized to each individual click, but the amplitude of the CNPs decreased along the train in a two-phase exponential pattern, reflecting the neural adaptation (fig. 5). This adaptive pattern varied as a function of stimulation rate and intensity with a faster decay as rate and intensity increased. These data for acoustic stimuli are fully in line with previous evoked potentials studies in VCN [Evans, 1975; Huang, 1981; Loquet and Rouiller, 2002; Loquet et al., 2003] and they are comparable to adaptive properties found for the AN [Peake et al., 1962; Eggermont and Spoor, 1973]. As a consequence, the acoustic adaptation in the VCN mainly reflects the adaptation present in the AN or more upstream, at the hair cell-nerve fiber synapse, where the major part of adaptation is thought to originate [Eggermont, 1975; Furukawa and Matsuura, 1978; Furukawa et al., 1978]. At this level, direct evidence for adaptive mechanisms are still lacking and authors have therefore tempted to model adaptation. For example, Smith and Brachman [1982] suggested that adaptation is produced by the depletion in cascade of neurotransmitter located in three pre-synaptic stores. This model is able to reproduce the three-phased acoustic adaptation where increments and decrements in intensity are taken into account. However, there is clear evidence now that the events taking place at the hair cell-nerve fiber synapse do not account for the entire adaptation observed in the AN. Indeed, the present data derived from direct electric stimulation of the AN showed a weak adaptation at low stimulation rates (100-200 pps), which became larger at stimulation rates above 400 pps, although still less pronounced than the

adaptation observed for acoustic stimuli (fig. 5). Furthermore, the electric adaptive decay appeared less sharp than that obtained with acoustic stimuli especially within the initial 5 ms of the train whereas the last 200 ms led to a progressive additional adaptation until a quasi steady-state was reached. These results regarding adaptation to electric stimulation of the cochlea are fully consistent with previous descriptions based on AN evoked potentials in animals [Haenggeli et al., 1998; Matsuoka et al., 2000] and intracochlear recordings in humans [Wilson et al., 1997], confirming that adaptive phenomena are still present even when the hair cells and the afferent synapses were bypassed. The remaining adaptation is probably mainly related to the refractoriness of AN fibers. Indeed, the eCNPs recorded in the present study represent the summed activity of several subpopulations of CN, which have different refractory properties. Therefore, in response to a train of pulses presented at high rate (for instance 800 pps), a subpopulation of CN neurons that responded to the first pulse will not be able to respond to the second pulse of the train, resulting in a strong decrease of the eCNP as compared to the eCNP to first pulse. The units which did not respond to the second pulse recovered and can therefore respond to the third pulse, producing a larger eCNP than to the second pulse, thus corresponding to the initiation of the alternation phenomenon (fig. 7), which strongly depends on pulse rate, in line with the previous study of Matsuoka et al. [2000]. At low repetition rate (100 pps), the interpulse interval is sufficient for full recovery of all units since, according to Brown [1994], the relative refractory period of the AN may last not more than 5 ms. This absence of adaptation was previously established in the VCN through both extracellular [Glass, 1984; Maffi et al., 1988] and intracellular recordings [Paolini and Clark, 1998; Babalian et al., 2003]. Based on these results, one may therefore suggest that the adaptation curves obtained with repetitive acoustic clicks at 100 pps exhibited mainly an adaptation due to transmitter release by hair cells (fig. 5, left

panels). Thus, when considering mathematical model for adaptation, pre- and post-synaptic events, as well as refractory mechanisms in the AN may be included (Eggermont [1985]; Meddis [1988]). However, one must keep in mind that these mechanisms cannot completely explain the eCNP adaptation patterns and fatigue of the nerve is not excluded nor a survival of hair cells at regions apical to the cochlear implanted electrode [Hu et al., 2003].

CNP to modified electric pulse trains

In contrast to acoustic responses, the adaptive patterns obtained in response to electric stimulation in the 30-70 μA range were less influenced by the level of stimulation (fig. 6), whereas individual eCNP magnitudes were largely intensity-dependent (fig. 5). One reason for such a difference is probably that the intensity of the electric stimulus in the chosen range is directly proportional to the number of highly synchronized responding fibres, whereas acoustic stimuli activate many units of different thresholds through a transduction apparatus which results in a weaker synchronization [Prijs, 1975]. Because less eCNP than aCNP adaptation is obtained when using an electric stimulation with a current burst of constant intensity, we tested therefore, in the second part of the present study, intensity-modified electric pulse trains in order to obtain a neural adaptation comparable to that observed with acoustic stimulation. The results illustrated in figure 9 show that, when stimulating the cochlea with a modified train of electric pulses of exponentially decreasing intensity, an adaptive pattern close to the natural phenomenon observed for acoustic stimulation can be obtained, in particular from 200 pps to 1000 pps. Therefore, the envelope of the response has mirrored the shape of the electric stimulus and an abrupt decrease of the intensity during the first milliseconds of the stimulating train produced the desired adaptive pattern by diminishing

mainly AN fibers recruitment. Nevertheless, it is noticeable that at low stimulation rate (100 pps), the curve established with the modified train of electric pulses revealed a more pronounced adaptation than that obtained with acoustic stimulation (fig. 9). This observation demonstrates that the equation used to modify the electric stimulus in the present study is not adapted to all repetition rates, especially when little or no neural refractoriness is involved as it is the case at low repetition rates. Based on these considerations, further studies are underway in the laboratory aimed at improving the current electric stimulation strategy.

Conclusion

In conclusion, although there is still uncertainty about the sound processing strategy which leads to the best discriminating abilities, the results of the present study emphasize the benefit which may be obtained from incorporating modified electric pulse trains in cochlear prosthesis processors to mimic the adaptive neural response patterns to natural acoustic stimulation. Indeed, because the adaptation process contributes largely to accentuate rapid changes in stimulus composition (speech transients) [Kiang et al., 1979], we propose that adding such a process in human cochlear implanted prosthesis may substantially improve speech discrimination and intelligibility in noisy environments.

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Legend to figures

Fig. 1. Illustration of the subtraction method used to measure the amplitude of the response (N_1 - P_1) in near-field evoked potentials to individual clicks delivered in a train. The columns from left to right show the number of clicks in the train, the raw responses evoked by the corresponding number of clicks ("Record"), the subtraction performed (e.g. trace 2 - trace 1), and the resulting waveforms ("Result"). Data are from Rat #4 and were obtained with clicks presented at the rate of 600 pps, at an intensity of 50 dB SPL. The first 10 ms of the train are shown and negative polarity is downward. The dashed line points to the "uncontaminated" response to the 2nd, 3rd, 4th and 5th click in the train, from top to bottom in the rightmost column.

Fig. 2. Photomicrographs of frontal sections through the brain stem showing the location of the tip of the chronic recording microelectrode in the left ventral cochlear nucleus of two implanted rats: (A) Rat #1, (B) Rat #2. an: auditory nerve; VCN: ventral cochlear nucleus; Pfl: paraflocculus. The dotted arrow represents the electrode track. Scale bar: 300 μ m.

Fig. 3. Typical ventral cochlear nucleus near-field evoked potentials recorded from the same chronic monopolar intracranial electrode in one animal (Rat #3).

(A) Auditory evoked potentials (aCNP) elicited by 250 ms trains of repetitive rectangular acoustic clicks (100 μ s) presented at a rate of 100 pulses per second. (B) Electrically evoked potentials (eCNP) elicited by 250 ms trains of repetitive biphasic square pulses (50 μ s/phase, anodic-first) applied to monopolar intracochlear electrode at a rate of 100 pulses per second. No stimulus artefact cancellation procedure was used and the artefacts (asterisk) were at most 5 times larger than the compound action potential height. For clarity's sake, artefact were graphically reduced.

In both panels, only the first 35 ms of the train are shown. In addition, the trace at the highest intensity exhibits an expanded time scale (bottom graph) which demonstrates the response to an individual pulse. N_1 , P_1 and N_2 deflections are easily recognisable (negativity polarity is downward). Stimulus intensity is given to the upper right of each response curve.

Fig. 4. Summary of wave N_1 and wave N_2 latencies (measured at the peak) derived from the four rats (6 measures per animal) in response to acoustic (A) or electric (B) stimulation. Interwave latencies were calculated from N_1 and N_2 latency mean values and are indicated on the right of the vertical bars. The error bars represent the standard deviation from the mean latency value.

Fig.5. Amplitudes of ventral cochlear nucleus near-field potentials normalized relative to the largest potential observed (usually the potential to the first pulse, at the highest stimulus level) evoked by acoustic stimulation (in the left column) or electric stimulation (in the right column). The recordings were obtained from the same chronic monopolar intracranial electrode in one animal (Rat #4) and the potential amplitudes were displayed as a function of the position of the individual stimulating pulses along the 250 ms train. For each of the pulse rates

ranging from 100 to 1000 pps, three intensities are presented: 50, 30, 10 dB SPL and 70, 50, 30 μ A, for acoustic and electric stimulation, respectively.

Fig. 6. Same data as in figure 5 but with N_1 - P_1 amplitudes normalized relative to the largest potential observed at each intensity tested (usually the potential to the first pulse). As an example, responses evoked by electric stimulation are presented at repetition rate of 100, 600 and 1000 pps and at intensities of 70, 50, 30 μ A. The potential amplitudes were displayed as a function of the position of the individual stimulating pulses along the 250 ms train.

Fig. 7. Phenomenon of alternation (oscillation) of the N_1 - P_1 amplitudes of ventral cochlear nucleus near-field potentials evoked by acoustic stimulation (left side) or electric stimulation (right side). Data are derived from Rat #4 at the rate of 800 pulses per second and presented with an expanded time scale where only the first 20 ms are shown.

Fig. 8. Schematic representation of construction of the modified electric stimulus. The upper left panel shows N_1 - P_1 amplitudes of ventral cochlear nucleus near-field potentials evoked, for instance, by a 30 dB SPL repetitive clicks delivered at a rate of 100 pulses per second (the acoustic click train is represented diagrammatically along the x-axis). Each amplitude point was first reported on the electric growth function established before for the same animal (lower left panel) in order to determine the electric stimulus intensity required to elicit the same response amplitude. The resulting transformation was displayed as a function of the position of the point along the 250 ms train and is depicted in the right panel. The mathematical description of the curve allowed to determine two time constants (K_1 and K_2), two y intercepts (y_1 and y_2) and one plateau (Plateau) which were fed into an application development computer

system in order to produce the corresponding exponentially decaying electric stimulus.

Fig. 9. Amplitudes of ventral cochlear nucleus near-field potentials normalized relative to the largest potential observed in the train (usually the response to the first pulse) evoked by 30 dB SPL acoustic clicks (red curve), 50 μ A steady electric pulses (black curve) and modified electric pulses (blue curve) in one animal (Rat #4). For each of the pulse rates ranging from 100 to 1000 pulses per second, amplitudes were displayed as a function of the position of the stimulating pulse in the 250 ms train.

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Table 1

Statistical comparison of adaptation curves elicited by acoustic and electric or modified electric pulse trains as a function of stimulus rate

Rate (pps)	Acoustic _{30 dB SPL} - Electric _{50 μA} ^a			Acoustic _{30 dB SPL} - Modified Electric ^a		
	F	Df	P value	F	Df	P value
100	2.191	36	0.0002	2.271	36	0.0068
200	2.235	60	<0.0001	1.536	60	0.2737 [†]
400	2.712	54	<0.0001	1.546	54	0.3059 [†]
600	1.470	66	<0.0001	1.613	66	0.0365 [†]
800	3.095	78	<0.0001	1.872	78	1.0000 [†]
1000	1.422	90	0.0190	3.476	90	0.9595 [†]

^a Two-way analysis of variance tests the null hypothesis that there is no interaction between the two groups

[†] The two curves are not significantly different (confidence level set to 99%)

Figure 1

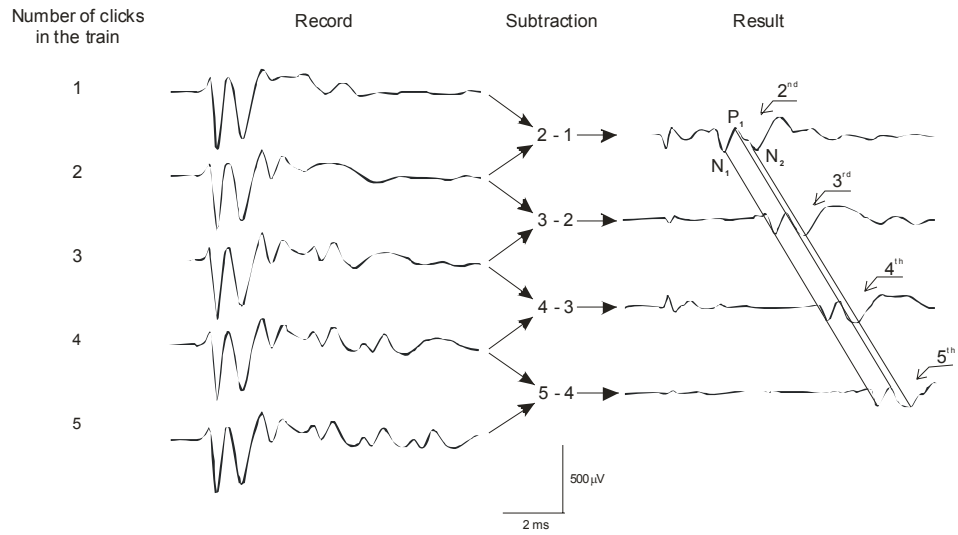


Figure 2

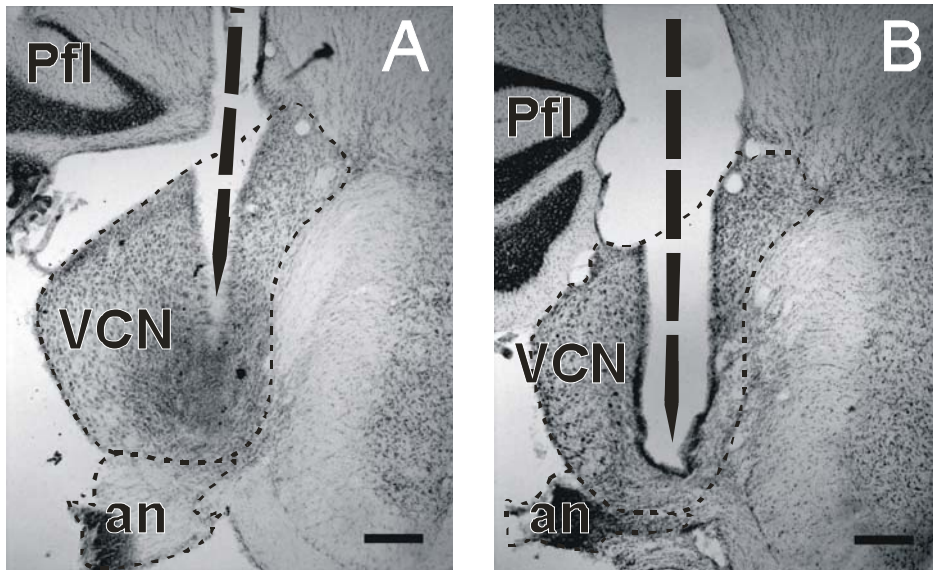


Figure 3

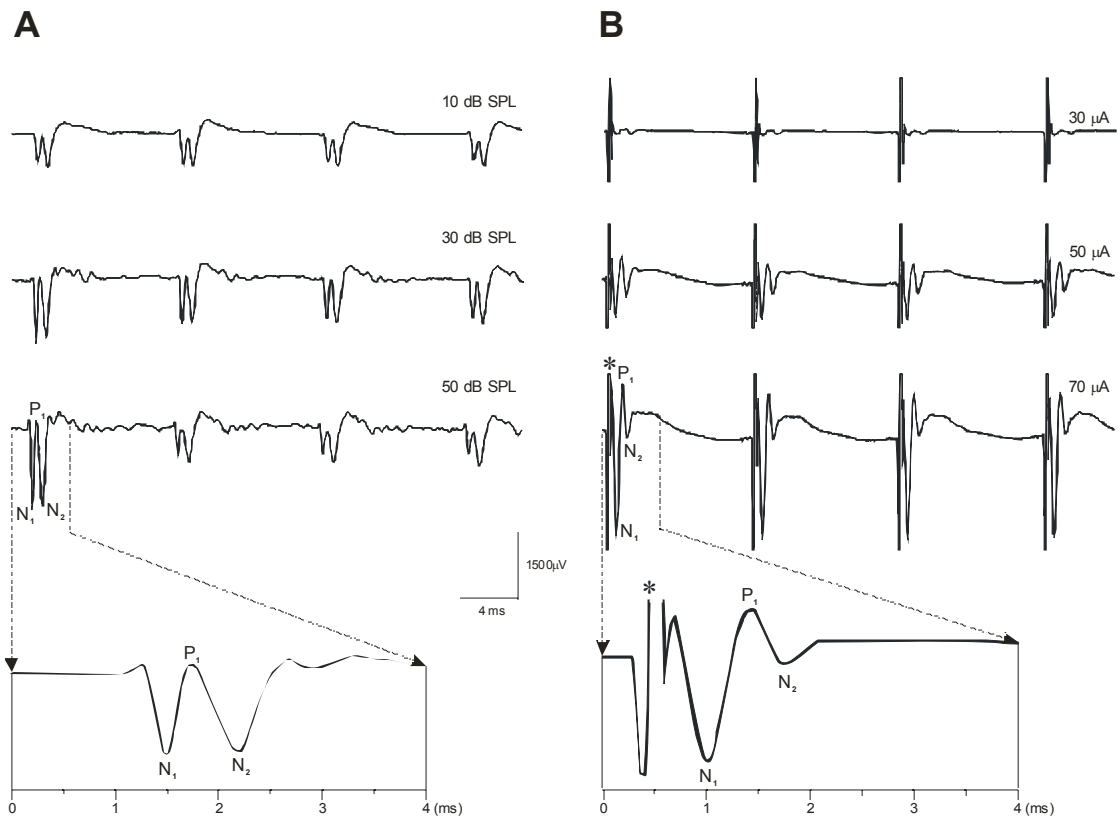


Figure 4

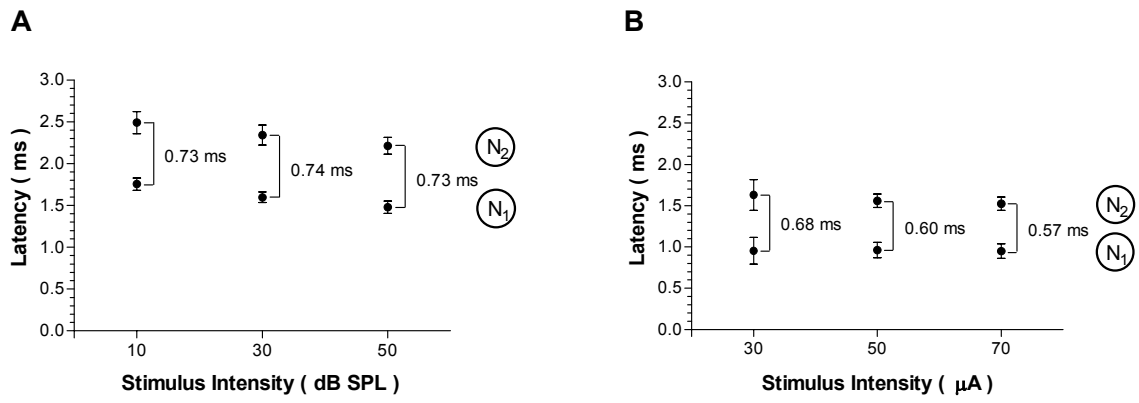
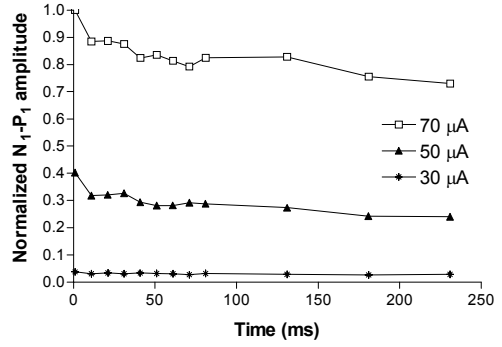
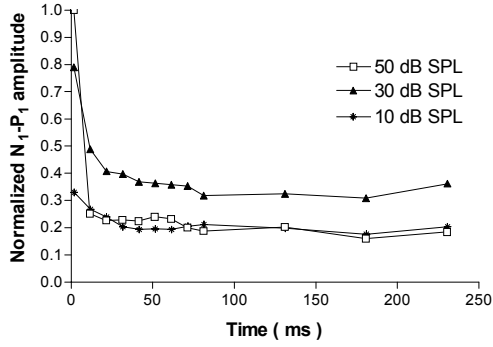
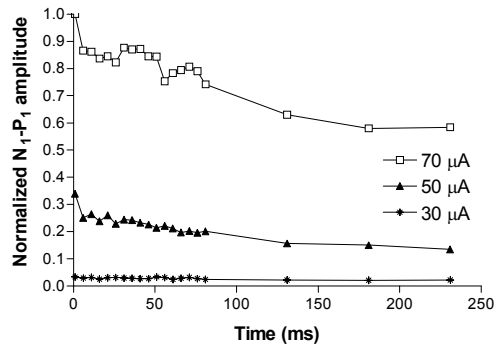
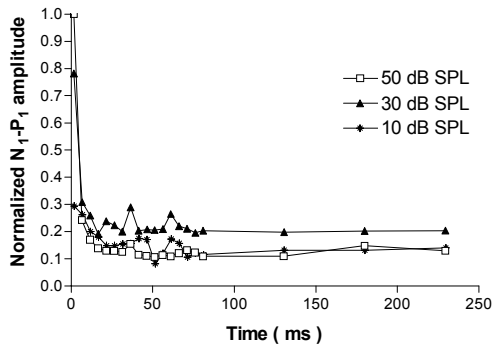


Figure 5 A

100 pps



200 pps



400 pps

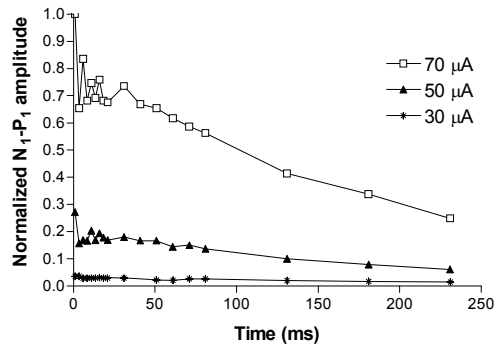
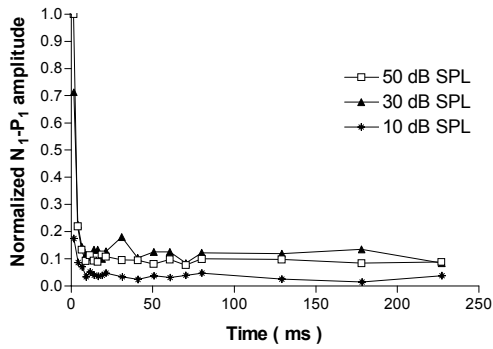
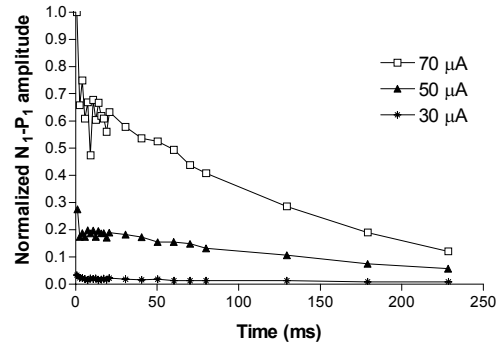
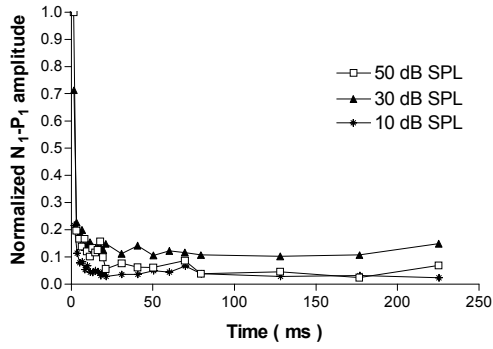
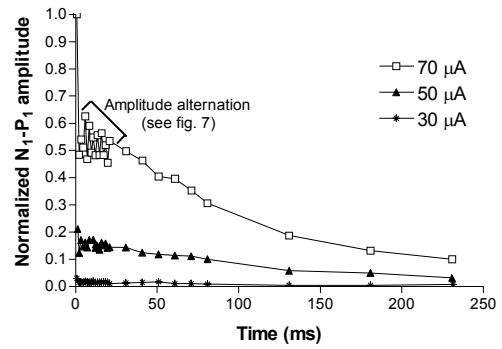
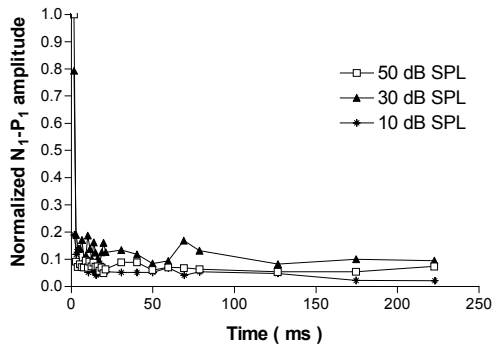


Figure 5 B

600 pps



800 pps



1000 pps

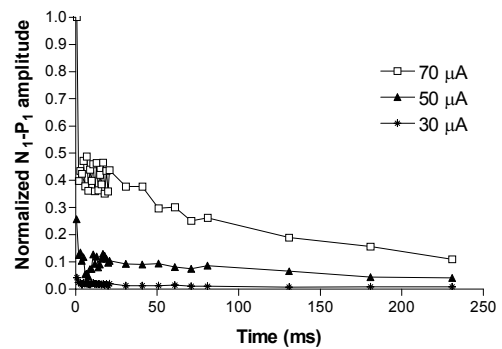
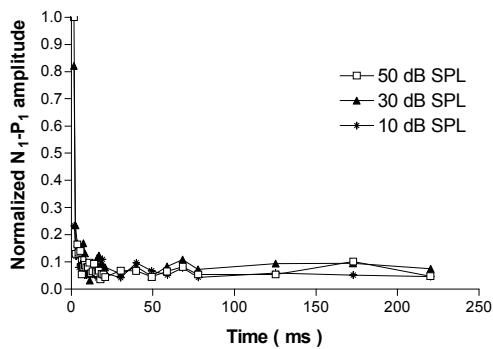
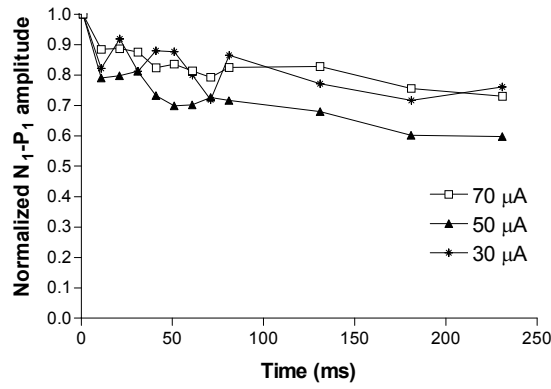
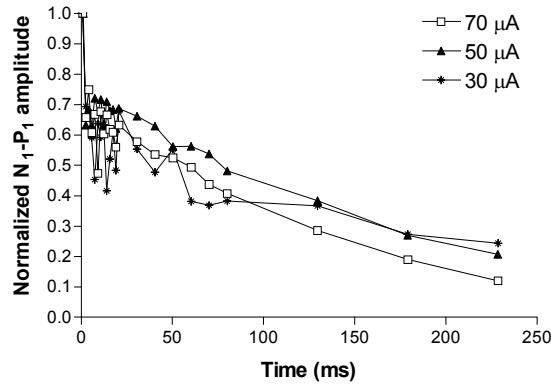


Figure 6

100 pps



600 pps



1000 pps

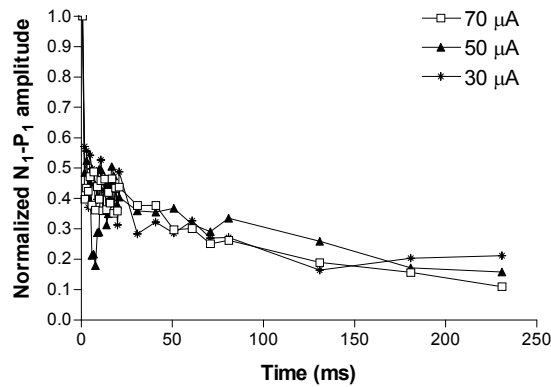


Figure 7

800 pps

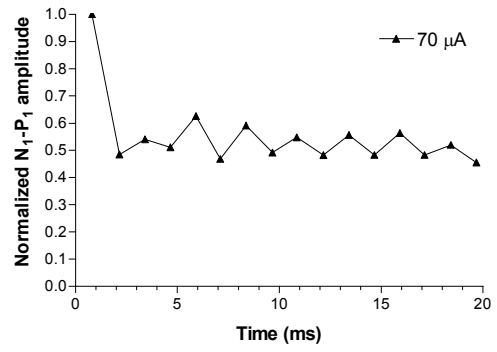
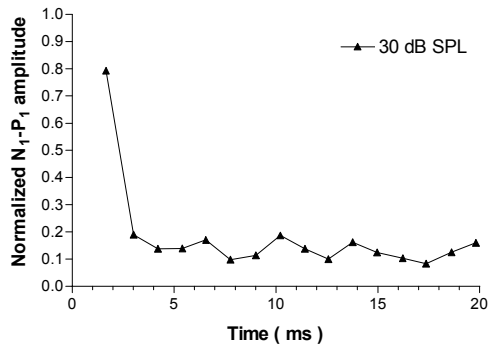


Figure 8

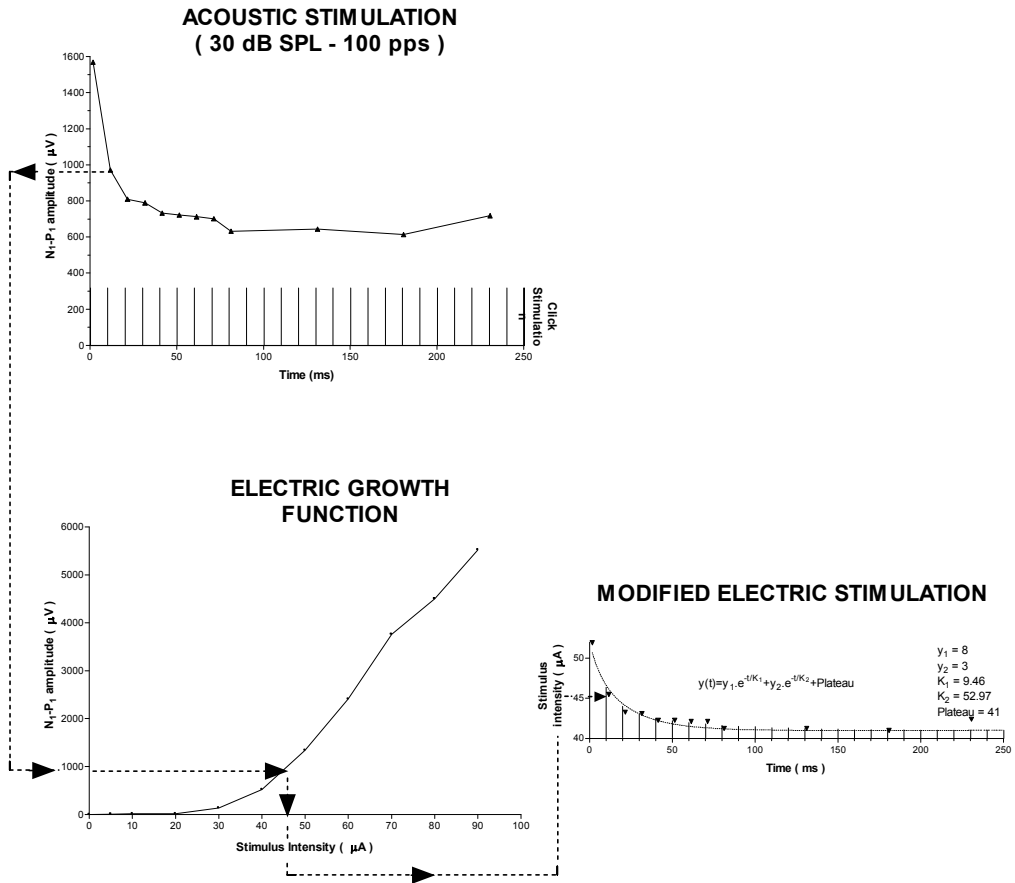


Figure 9

