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Direct comparison between properties of adaptation of the auditory nerve and the ventral cochlear nucleus in response to repetitive clicks

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Abstract

The present study was designed to complete two previous reports [Loquet, G., Rouiller, E.M., 2002. Neural adaptation to pulsatile acoustical stimulation in the cochlear nucleus of the rat. Hear. Res. 171, 72–81; Loquet, G., Meyer, K., Rouiller, E.M., 2003. Effects of intensity of repetitive acoustic stimuli on neural adaptation in the ventral cochlear nucleus of the rat. Exp. Brain Res. 153, 436–442] on neural adaptation properties in the auditory system of the rat. Again, auditory near-field evoked potentials (ANEPs) were recorded in response to 250-ms trains of clicks from an electrode chronically implanted in the ventral cochlear nucleus (VCN). Up to now, our interest had focused on the adaptive behavior of the first one (N_1) of the two negative ANEP components. A re-examination of our data for the second negative component (N_2) was now undertaken. Results show that the adaptation time course observed for N_2 displayed the same three-stage pattern previously reported for N_1. Similarly, adaptation became more pronounced and occurred faster as stimulus intensity and/or repetition rate were increased. Based on latency data which suggest N_1 and N_2 to be mainly due to the activity of auditory-nerve (AN) fibers and cochlear nucleus neurons, respectively, it was concluded that neural adaptation assessed by gross-potentials was similar in the AN and VCN. This finding is meaningful in the context of our search to restore normal adaptation phenomena via electro-auditory hearing with an auditory brainstem implant on the same lines as our work in cochlear implants.

Keywords: Auditory evoked potentials; Brainstem; Click; Rat; Unanaesthetized

1. Introduction

Adaptation properties of primary auditory neurons have been assessed by several authors having recorded either compound action potentials (Peake et al., 1962a,b; Eggermont and Spoor, 1973; Gorga and Abbas, 1981; Abbas, 1984; Chimento and Schreiner, 1990, 1992) or firing patterns from single auditory-nerve fibers (Kiang et al., 1965a; Smith and Zwislocki, 1975; Smith, 1977, 1979; Harris and Dallos, 1979; Westerman and Smith, 1984; Yates et al., 1985; Rhode and Smith, 1985; Chimento and Schreiner, 1991; Javel, 1996; Taberner and Liberman, 2005), in response to either long pure tones or trains of repetitive tone bursts or clicks. The adaptation time course displayed by primary auditory neurons was described to consist essentially of three stages: a rapid decrease of compound-action-potential amplitude or firing rate during the first few milliseconds of stimulation (rapid adaptation), followed by a slower decrease (short-term adaptation) and, finally, a steady state. Using

Abbreviations: AN, auditory nerve; ANEP, auditory near-field evoked potential; CF, characteristic frequency; CN, cochlear nucleus; N_1, first negative ANEP component; N_2, second negative ANEP component; P_1, first positive ANEP component; pps, pulses per second; VCN, ventral cochlear nucleus

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even longer stimuli, a long-term (s) and a very-long-term (min) adaptation component were also described (Javel, 1996).

As opposed to those of primary auditory neurons, adaptation patterns of cochlear nucleus (CN) units to pure-tone bursts are very diverse. Many different response types are generated in the CN, such as primary-like, primary-like with notch, and chopper units, among many more (e.g. Kiang et al., 1965b; Pfeiffer, 1966; Evans, 1975). Evoked potentials recorded from the ventral cochlear nucleus (VCN) displayed an adaptive behavior also in response to short repetitive pure-tone bursts (Huang and Buchwald, 1980; Huang, 1981) or click trains (Loquet and Rouiller, 2002; Loquet et al., 2003). These latter two studies carried out in our laboratory demonstrated that the first negative component (N_1) of the auditory near-field evoked potentials (ANEPs) recorded from the VCN at various stimulus repetition rates and intensities displayed three adaptation stages comparable to those described above for primary auditory neurons (rapid adaptation, short-term adaptation, steady state). Based on the location of the recording electrode (in the VCN), one may be tempted to conclude that primary auditory and VCN neurons exhibit similar adaptive behaviors. However, the ANEPs recorded from the VCN were characterized by the presence of multiple consecutive components whose precise origins remain a matter of debate (e.g. Møller, 1983; McMahon et al., 2004). In particular, when recorded from the VCN, the ANEPs exhibit a prominent second negative component (N_2), nearly as large as the first negative component. Moreover as will be argued in the discussion section, when comparing our latency data to that of single-unit recordings carried out by various authors, it seems most probable that the first and the second negative components of ANEPs recorded from electrodes in the VCN are mainly due to the activity of AN fibers and VCN neurons, respectively. The present study aimed at investigating the adaptation properties of N_2, allowing for a direct comparison in the same experimental conditions with the properties derived from N_1 (Loquet and Rouiller, 2002; Loquet et al., 2003). The working hypothesis is that, if the adaptive properties of N_1 and N_2 were comparable, the conclusion that primary auditory and VCN neurons do not differ with respect to adaptation would receive stronger support. In contrast, if N_1 and N_2 exhibit different adaptive properties, the possibility that the synaptic transmission between primary auditory neurons and VCN neurons may modify the adaptation to repetitive acoustic stimuli has to be considered.

The clinical implication of these adaptation studies lies in the field of cochlear and brainstem auditory implants. Recently, in a study carried out in our laboratory, a stimulus paradigm consisting basically of varying repetitive electrical pulses rates was developed to stimulate the AN (via a simplified cochlear implant) and evoke AN-fiber response envelopes resembling those observed in response to repetitive acoustic stimulation as closely as possible (Loquet et al., 2004). Based on the results of the present study, we think that the testing of such a stimulus paradigm may yield realistic adaptation response envelopes in local neurons also when applied directly to the VCN (via a simplified auditory brainstem implant).

2. Materials and methods

The methodological procedures are the same as those described in detail in two previous reports (Loquet and Rouiller, 2002; Loquet et al., 2003). Briefly, experiments were conducted on male adult Long-Evans rats (Janvier Laboratories, France) weighing approximately 300 g ($n = 6$). ANEPs were recorded from a chronic electrode implanted in the left VCN (Fig. 1a). During stimulation, animals were not anaesthetized but only lightly sedated (levomepromazin, 10 mg/kg i.p.). The experimental procedure was approved by the Swiss veterinary authorities and was performed in accordance with the "Principles of laboratory animal care" (NIH Publication No. 86-23, revised 1985) and the 1964 Declaration of Helsinki for animal care.

ANEPs were recorded in response to trains (250 ms duration) of repetitive clicks (100 μs duration) delivered at six different repetition rates (100, 200, 400, 600, 800, and 1000 pulses per second (pps)) and five different intensities (5, 10, 30, 50, and 70 dB SPL). TDT (Tucker Davis Technologies) System II acoustic stimulation and data acquisition software (BioSig32) was used to automate ANEP averaging over 50 stimulus-train presentations and to store the recorded traces for off-line analysis. Each click train was separated from the next one by a pause (silence) of 250 ms (50% duty cycle). ANEPs were amplified (2×10^3) and bandpass-filtered between 30 Hz and 3 kHz. A typical recording is presented in Fig. 1b. The goal of the present study was to analyze the N_2 component of the ANEPs recorded from the VCN by assessing the voltage difference between the peaks P_1 and N_2. At repetition rates higher than 400 pps, responses to individual clicks started to overlap so that the amplitude of a given response was influenced by the preceding one. In order to circumvent this contamination, a subtraction method was used (Wilson et al., 1997; Loquet and Rouiller, 2002; Loquet et al., 2003, 2004). This method consisted in presenting series of n clicks followed by series of $n + 1$ clicks (50 presentations of each), averaging them, and then subtracting the former from the latter, thus exposing the response to the $n + 1$ click. However, this technique would, especially at high repetition rates, require a very large number of stimulus sequences to isolate the ANEPs to every click in a given train. Therefore, in order to avoid over-stimulation during recording sessions, ANEPs were collected for all consecutive clicks during the initial 20 ms of stimulation, then for one click every 10 ms during the next 60 ms, and for only three individual clicks during the remaining 170 ms of a click train (Fig. 1c). All $P_1 - N_2$ amplitudes evoked by a given stimulus train were normalized relatively to the highest response in the sequence (usually the first one) and then

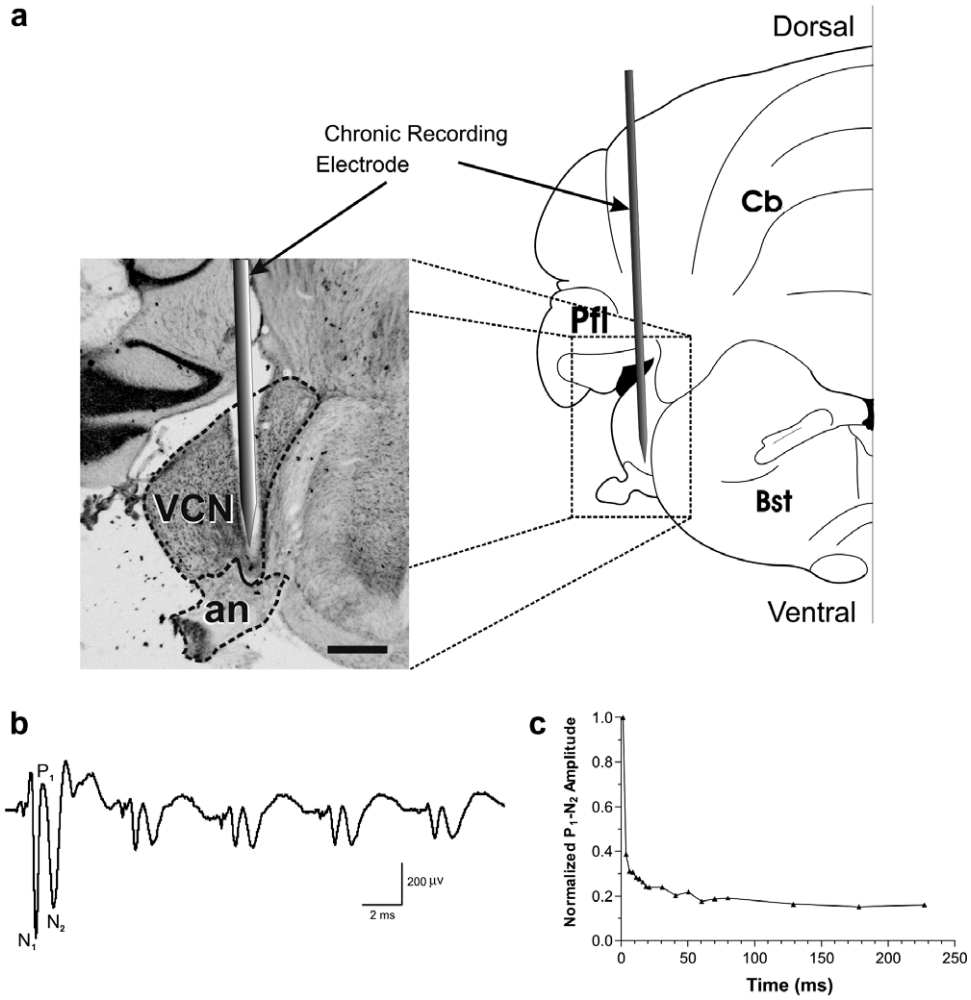


Fig. 1. (a) Drawing and photomicrograph of frontal section through the brainstem of one implanted rat (Rat 4) showing the location of the tip of the chronic recording microelectrode in the left ventral cochlear nucleus. an, auditory nerve; VCN, ventral cochlear nucleus; Pfl, paraflocculus; Cb, cerebellum; Bst, brainstem. Scale bar: 500 µm. (b) ANEPs elicited by a 250 ms duration train of repetitive clicks presented at 70 dB SPL and a rate of 200 pps (Rat 6). Only the first 25 ms of the response are shown. (c) Adaptive properties of the N_2 component of the ANEPs (voltage difference between the peaks P_1 and N_2) during click trains presented to Rat 1 at 400 pps and 50 dB SPL. The amplitude of the response to each click in the train was normalized (set to 1 for the highest $P_1 - N_2$ peak to peak amplitude) and plotted as a function of the position (time) of the corresponding click in the train. The response was averaged for 50 trains of clicks presented.

plotted as a function of position of the evoking click within the train, thus displaying the changes in response amplitude as a function of time (Fig. 1c). The location of the recording electrode in the VCN was verified at the end of the experiment (three months after implantation) in all rats, following histological procedures previously described (Loquet and Rouiller, 2002).

3. Results

Our chronic recording electrodes aimed stereotaxically at the left VCN were positioned at the aimed location, as shown in the photomicrograph presented in Fig. 1a. Typical ANEPs recorded with such a chronic electrode are shown in Fig. 1b. They comprise a first negative-positive deflection (N_1 component), followed by a second negative deflection (N_2 component). The average latencies of the two negative peaks N_1 and N_2 are indicated in Table 1 as a function of stimulus intensity. The latencies of both peaks clearly decreased with increasing stimulus level, whereas the delay between them remained rather constant at around 0.8 ms.

Fig. 1b shows the ANEPs recorded in response to the first 5 clicks of a stimulus train presented at 200 pps and 70 dB SPL. Clearly, the amplitude of both the N_1 and the N_2 components (assessed as the voltage differences $N_1 - P_1$ and $P_1 - N_2$, respectively) was larger in response to the first click of the stimulus train than in response to the following ones, thus reflecting the phenomenon of adaptation. The time course of the amplitude decay of the N_2 component displayed three apparent stages: an initial fast drop (rapid adaptation), a slower decrease (short-term adaptation) and, finally, a steady state (Fig. 1c). Furthermore, this time course was rate-dependent as can

Table 1
Latencies of peaks N_1 and N_2 of the ANEP as recorded in the present study from electrodes positioned in the VCN of the rat as a function of stimulus intensity

Intensity	N_1 latency (ms)		N_2 latency (ms)		$N_2 - N_1$ (ms)	
	Mean	SD	Mean	SD	Mean	SD
5 dB SPL	1.87	0.05	2.67	0.07	0.80	0.06
10 dB SPL	1.79	0.05	2.60	0.07	0.81	0.08
30 dB SPL	1.65	0.04	2.45	0.05	0.81	0.06
50 dB SPL	1.49	0.04	2.29	0.06	0.79	0.04
70 dB SPL	1.39	0.07	2.17	0.10	0.78	0.08

Note. Latency values are derived from six rats. SD, standard deviation.

be derived from the upper panel of Fig. 2, which displays the adaptive behavior of N_2 as a function of stimulus repetition rate at constant stimulus intensity (30 dB SPL). Clearly, as repetition rate was increased, the initial drop in N_2 amplitude occurred faster and the steady state established itself at a lower level. The same adaptive behavior can be observed when considering data averaged from all six rats included in the present study (Fig. 2, middle panel). For comparison, the adaptation of the N_1 component reported earlier (Loquet and Rouiller, 2002; Loquet et al., 2003) is shown in the bottom panel of Fig. 2.

Fig. 3 displays the response behavior of the N_2 component of the ANEPs recorded from Rat 6 in response to click trains presented at all stimulus intensities and repetition rates tested. Again, going from low to high repetition rates, adaptation patterns clearly became more pronounced at all intensities. Furthermore, at each repetition rate, the adaptive behavior of the N_2 component was more prominent as stimulus intensity was augmented: the initial drop in amplitude occurred faster and steady-state amplitude was lower. Averaged data from all six animals are represented for the N_2 component, analogously to Fig. 3, in the left-hand panel of Fig. 4. In this figure, the curves obtained at stimulus levels of 5 and 10 dB SPL show that the adaptation pattern in response to low-intensity stimulation strongly depended on repetition rate: at 100 pps the two traces displayed steady-state amplitudes between 0.8 and 0.9 which dropped dramatically to below 0.3 at 1000 pps. For higher-intensity stimulation, rate effects were less marked: steady-state amplitude of the 50- and 70-dB-SPL traces decreased from around 0.35 at 100 pps to about 0.1 at 1000 pps. The 30-dB-SPL curve displayed a behavior intermediate to the two discussed above. Summarizing, the effect of stimulus repetition rate on adaptation was more pronounced at low than at high intensities and, consequently, the effects of stimulus intensity on adaptation patterns were more prominent for low- than for high-repetition-rate stimulation (compare top and bottom panels on the left-hand side of Fig. 4).

For comparison, corresponding data sets were plotted for the adaptation behavior of the N_1 component of the ANEPs in the right-hand panel of Fig. 4 (averaged data from all six animals). Both N_1 and the N_2 components displayed closely resembling three-stage adaptation time courses, with comparable rate and intensity effects. In either case, an increase in stimulus repetition rate or intensity caused adaptation to occur faster and to be more pronounced. However, one can notice minor differences between the adaptation patterns displayed by N_1 and N_2. Whereas at low repetition rates there seems to be a small but consistent tendency for the N_2 component to display less adaptation than the N_1 component, this relationship is reverse at high repetition rates: here, the steady-state amplitudes of the N_2 component were usually lower than those of the N_1 component. Going from top to bottom in Fig. 4, this change occurred progressively and was more pronounced for low- than for high-intensity stimulation. The two graphs representing the amplitudes measured at 600 pps are almost identical. Thus, stimulus repetition rate seems to have a slightly greater influence on the behavior of the N_2 component than on that of the N_1 component. This conclusion is supported by the traces shown in Fig. 2: the curves representing the amplitudes of the N_2 component (middle panel) are more widely spread than those representing the N_1 component (bottom panel).

In Fig. 5, the ratio between the amplitude of the steady state and the amplitude of the highest peak in a given train was plotted for both N_1 and N_2 as a function of click repetition rate for each intensity tested (note that in order to mathematically assess the amplitude of the steady state of an adaptation curve, the last four data points (between 80 and 230 ms) were averaged). The data confirm the statements made above: the behavior of the N_2 component tended to be more strongly influenced by repetition rate than that of the N_1 component, as is apparent from the greater slope of the curves representing the former component, especially at low-intensity stimulation. For 5, 10, and 30 dB SPL, this trend could be proven to be statistically significant (two-way ANOVA; $p < 0.05$). Considering the sometimes rather large standard deviations, this may seem somewhat surprising. It should be considered, however, that paired-value two-way ANOVA was carried out, always comparing the amplitudes of the N_1 and N_2 components obtained from the same animal at corresponding stimulus parameters. The graphs shown in Fig. 5 were produced for all individual rats (not shown); the trends described above were usually displayed by 5, sometimes even by 6 out of 6 animals.

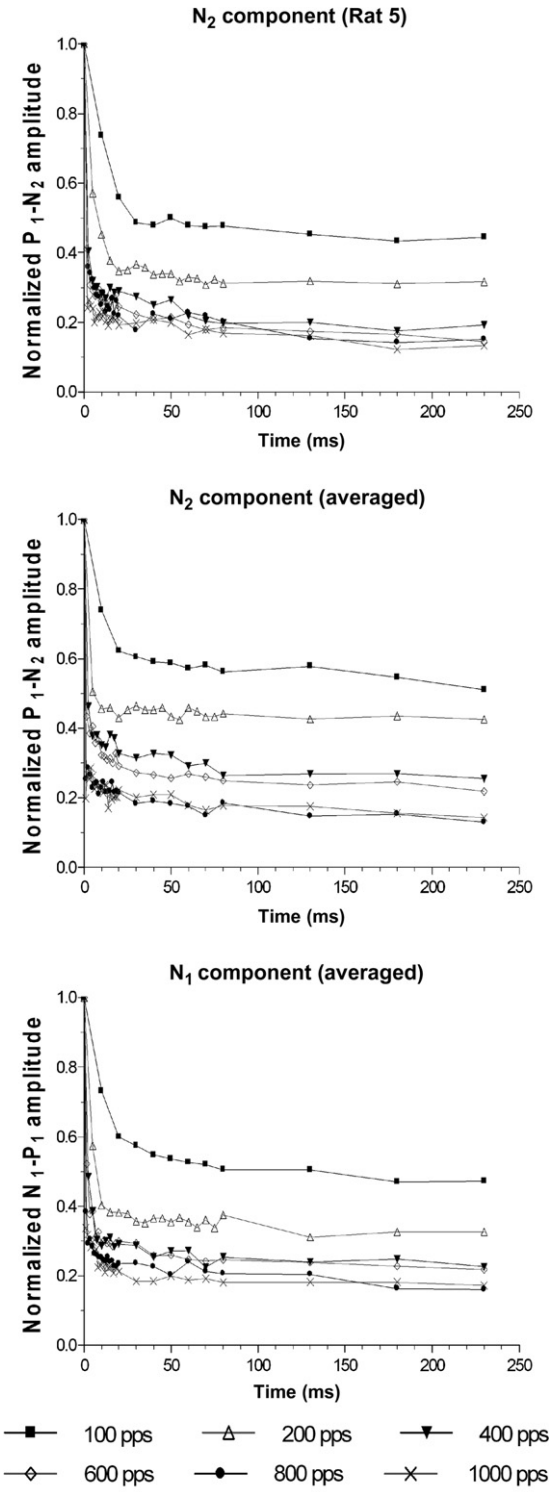


Fig. 2. Top panel: effect of stimulus repetition rate on the adaptation time course of the N_2 component of the ANEP. Data were recorded at 30 dB SPL from Rat 5. The amplitude of the response to each click in the train was normalized (set to 1 for the highest peak) and plotted as a function of the position (time) of the corresponding click in the train. The response was averaged for 50 trains of clicks presented at each repetition rate (as indicated in the bottom of the figure). Middle and bottom panels: comparison of the effects of stimulus repetition rate on the adaptation time courses of, respectively, N_1 (bottom panel) and N_2 (middle panel) from averaged data collected at 30 dB SPL from six animals.

In order to obtain the traces displayed in Fig. 6, the graphs in the right-hand panel of Fig. 4 were subtracted from their counterparts on the left (this was done only for intensities at or above 30 dB SPL). In other words, at the same time points along a train of clicks, the amplitude of the N_1 component was subtracted from the amplitude of the N_2 component of the ANEPs. In such subtraction graphs a negative value thus indicates that the N_2 component displayed more marked adaptation than the N_1 component at the corresponding time point. On the other hand, a positive value would reflect less adaptation of the N_2 component of the ANEPs when compared to N_1. The most striking feature of the traces in Fig. 6 is the negative peak immediately after stimulation onset displayed by practically all traces. In other words, adaptation right after stimulation onset was more pronounced for N_2 than for N_1 at almost all stimulus repetition rates and intensities. In quantitative terms, this difference was about 5–10% (again expressing the response amplitudes of the two components at these time points with respect to the respective highest response amplitudes in the given trains; Fig. 6). In contrast, Fig. 6 also shows that during the rest of the train up to stimulation offset, adaptation of the N_1 component was somewhat more pronounced than that of N_2.

4. Discussion

The present study allowed for a direct comparison between the respective properties of adaptation to repetitive clicks present in two consecutive negative components of the ANEPs recorded from an electrode placed in the VCN of un-anaesthetized rats. The advantage of the present paradigm is thus the possibility to compare in similar experimental conditions (same stimulation paradigm, same state of awareness, etc.) the properties of adaptation of distinct neural populations generating the N_1 and N_2 components of the ANEPs.

An approach to tentatively identify generators for the successive components of evoked potentials is the comparison of peak latencies with latency data of single neurons observed in various auditory structures (Møller, 1975, 1976, 1983; Friauf and Ostwald, 1988; FitzGerald et al., 2001; Paolini et al., 2001). The latency of auditory neurons depends on various parameters of both the stimulus used and the unit recorded from. Single-unit studies revealed, for example, that units with high characteristic frequency (CF) usually display shorter latencies than those with low CF (e.g. Kiang et al., 1965a; Møller, 1976; FitzGerald et al., 2001), due to the longer travel time of low-frequency stimuli along the basilar membrane. Moreover, latencies decrease as stimulus intensity increases (e.g. Møller, 1975; FitzGerald et al., 2001), likely due to the faster rise of the excitatory post-synaptic potential at higher stimulus levels (Møller, 1981a). Another explanation is the widening of the traveling wave along the basilar membrane with increasing intensities, resulting in a spread of excitation towards

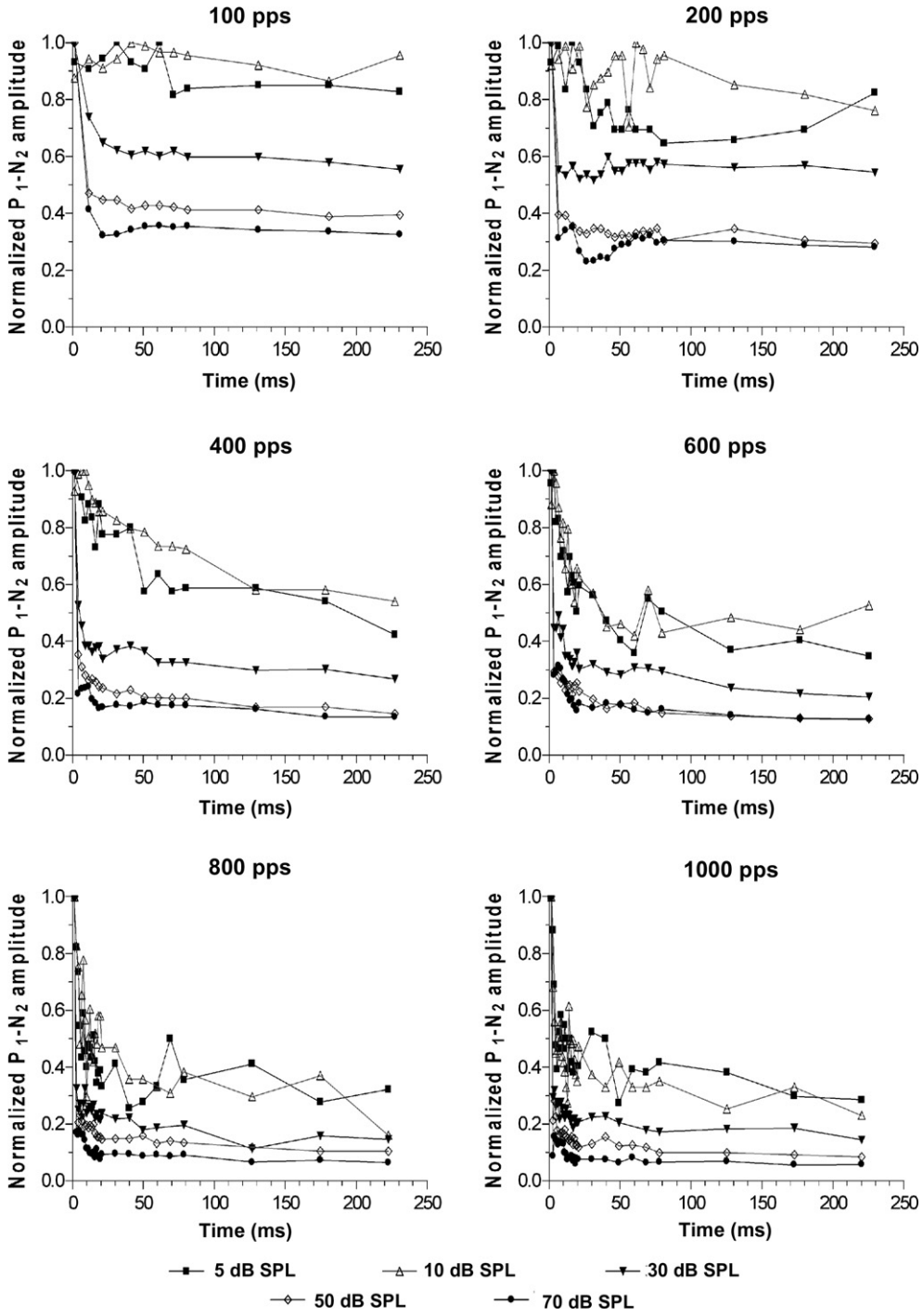


Fig. 3. The adaptation time course displayed by the N_2 component of the ANEPs is shown by plotting the normalized amplitude of the response to each click in the train as a function of its position (time) in the train. The different panels exhibit the effects of clicks repetition rate (as indicated above each panel) and intensity (as indicated in the bottom of the figure) on adaptation. Data are derived from Rat 6.

higher-CF regions of the cochlea. Furthermore, latency data vary across species and types of stimuli with, for instance, clicks usually yielding faster responses than tone bursts because the latter are characterized by a certain rise time, and threshold level is therefore reached after a certain delay. Finally, there is a considerable variability of axon diameter in the AN within the population of type-I primary auditory neurons (e.g. 2–6 μm in the cat; Arnesen and Osen, 1978) resulting in varying propagation velocities.

The latencies of the N_1 and N_2 components as obtained in the present study (Table 1) can be compared with existing single-unit latency data for the AN and the CN (Table 2: all studies mentioned were carried out in the rat). The N_1 peak latencies are generally consistent with single-unit latencies reported from primary auditory neurons (Table 2A). Therefore, it seems probable that the N_1 component of the ANEPs we recorded from the VCN predominantly represents the activity of AN fibers entering the CN in

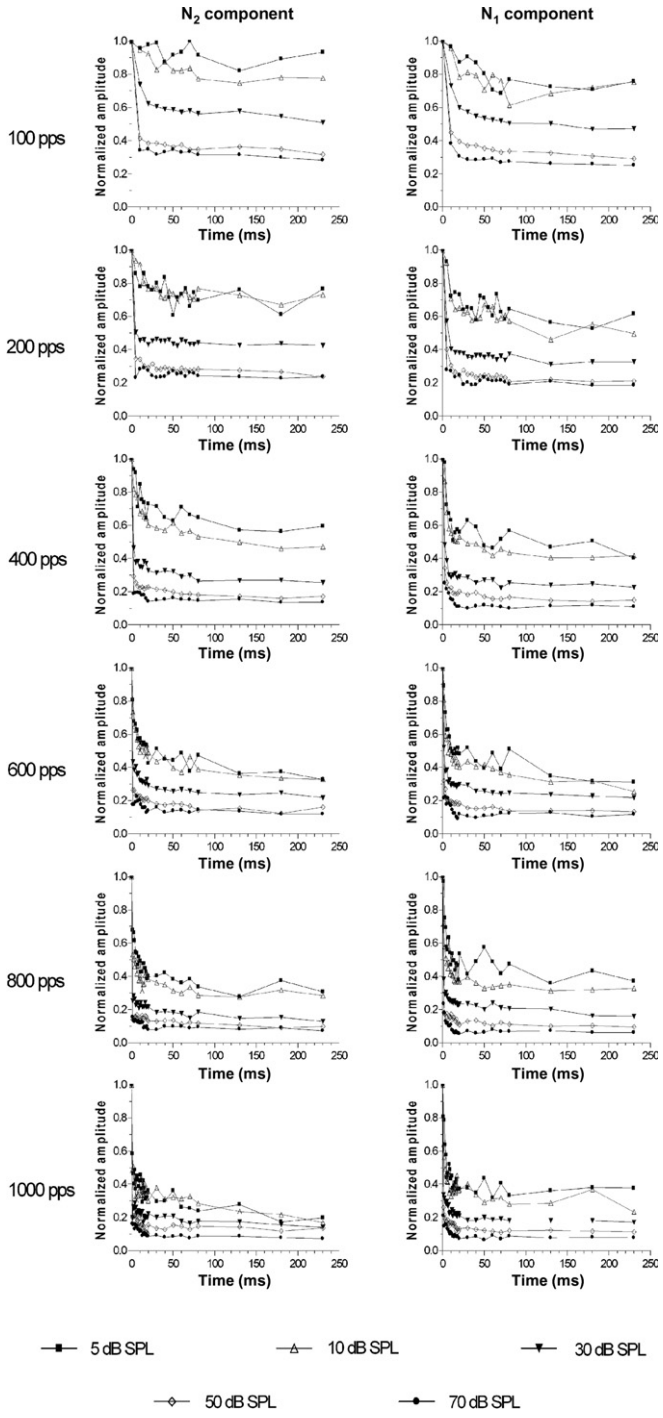


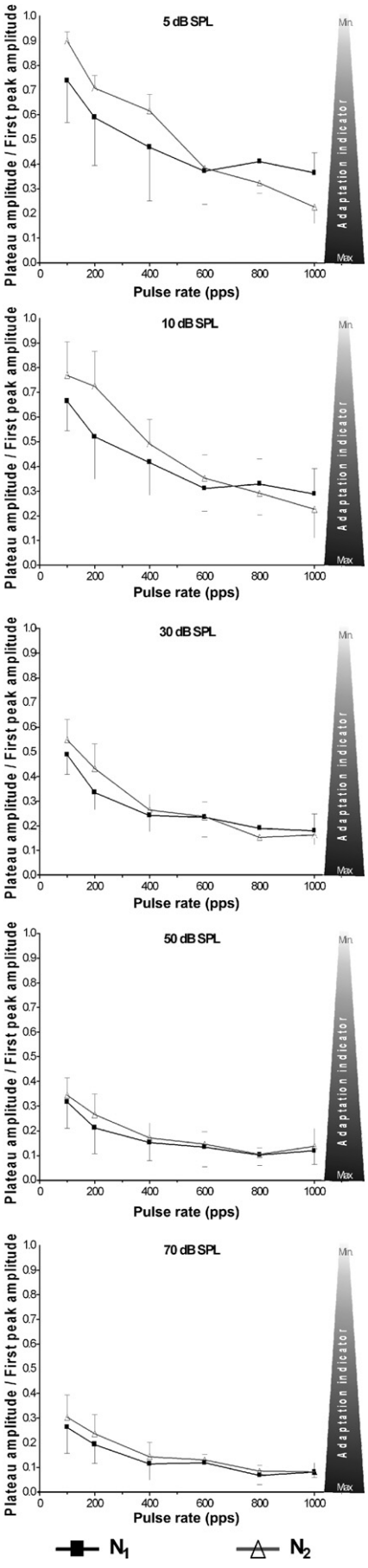
Fig. 4. Direct comparison of adaptation time courses as displayed by the N_1 component (right column) and the N_2 component (left column). Data averaged from all six animals. Same conventions as in Fig. 3.

proximity. The N_2 peak latencies of the ANEPs, on the other hand, are in line with most of the latency values reported for CN units (Table 2B). The N_1 and N_2 components are thus likely to be dominated by the consecutive activities of the AN and the VCN, respectively. Assuming this to be correct, the positive component P_1 of the ANEPs may represent the so-called pre-potential sometimes observed in single-unit recordings from primary-like units (e.g. Kiang et al., 1965b). This pre-potential sometimes precedes the action potential of primary-like units located in the VCN and is believed to represent the depolarization at the level of the endbulbs of Held (Bourk, 1976; Romand and Avan, 1997).

The latencies reported here for N_1 and N_2 are in line also with previous observations derived from evoked potentials. In auditory brainstem recordings, Shaw (1990) measured respective latencies of 1.27 and 1.99 ms for these two peaks. Considering his stimulus level to exceed even our highest stimulus intensities, these values are in good agreement with the ones we found at 70 dB SPL (Table 1). Møller (1981a,b, 1983), recording evoked potentials either from the round window or from the CN, also found waveforms and peak latencies well comparable to ours. Both Shaw (1990) and Møller (1981a,b, 1983) suggested the CN to be at the basis of N_2. Møller (1983) substantiated this hypothesis by comparing traces obtained before and after removal of the CN. After ablation of the CN, the trace recorded at the round window changed from a triphasic (N_1, P_1, N_2) to a monophasic, negative potential. The difference between the two curves, a trace exposing two peaks of opposite polarization, was thus supposed to reflect the activity of CN neurons.

In a recent study, McMahon et al. (2004) presented data at variance from the results of Møller (1983). When the activity of secondary auditory neurons was selectively blocked (in this case by cooling rather than removal of the CN), a larger P_1 component could be observed in evoked-potential recordings from the round window, implying that at least this positive component could not originate from the CN, as Møller (1983) had suggested. Although the N_2 component of the round-window potentials was abolished after cooling of the CN, McMahon et al. (2004) suggested this wave to be cochlear in origin because its amplitude and polarity did not change when the reference electrode was set at very different positions with respect to the CN. Note, in any case, that this whole argument refers to evoked potentials recorded from the round window whereas our recordings were derived from electrodes placed in the VCN. When deriving potentials from the CN, McMahon et al. (2004) recorded a response wave they attributed to local (secondary) auditory neurons, this response wave having a response latency similar to the N_2 component recorded from the round window.

Under all above assumptions, it seems appropriate to assume N_1 and N_2 to mainly represent the respective activities of primary auditory and CN neurons. Therefore, previous observations about the adaptive behavior of the first negative component of the ANEPs recorded from the VCN (Loquet and Rouiller, 2002; Loquet et al., 2003) are likely to predominantly reflect the properties of AN adaptation without, however, permitting novel conclusions on adaptation in the CN. The present study, introducing the adaptive properties of the second negative component of the ANEPs, is more likely to reflect adaptation characteristics of neurons in the VCN.



The VCN mainly consists of spherical and globular bushy cells as well as stellate cells (e.g. Osen, 1969; Brawer et al., 1974; Cant and Morest, 1979; Hackney et al., 1990). Intracellular single-unit studies have associated these three cell types with primary-like, primary-like with notch, and chopper responses, respectively (Rhode et al., 1983; Rouiller and Ryugo, 1984; Smith and Rhode, 1987; Smith et al., 1991, 1993; Ostapoff et al., 1994; for a review see Rouiller, 1997; Romand and Avan, 1997). At least the gross envelope of these responses (as implied in part by their names) is comparable to the one typically observed in AN fibers. Indeed, both the endbulbs of Held and the modified endbulbs (AN terminals contacting spherical and globular bushy cells in the VCN, respectively; e.g. Feldman and Harrison, 1969; Ryugo and Fekete, 1982; Rouiller et al., 1986) are classically thought to be very reliable (see e.g. Bourk, 1976; Romand and Avan, 1997), meaning that practically every action potential arriving at the pre-synaptic terminal is actually conducted to the post-synaptic membrane. This is also evident, for example, from the very comparable phase-locking properties observed in the AN and the anteroventral CN (e.g. Rouiller, 1997).

In general (Figs. 2 and 4), the adaptive properties of the second negative component of the ANEPs, as found in the present investigation, matched those of the first negative component in the same experimental conditions (Loquet and Rouiller, 2002; Loquet et al., 2003) and those previously reported for the AN (e.g. Peake et al., 1962a,b; Eggermont and Spoor, 1973; Harris and Dallos, 1979; Chimento and Schreiner, 1990, 1991; Westerman and Smith, 1984). Therefore, statements about the similarities in response patterns displayed by AN fibers and neurons typically found in the VCN can be extended in the sense that they do not only respond alike to single tone bursts but also in response to repetitive acoustic stimulation, even when stimulation rate and intensity are varied. This extension of similarity is of importance because of the implica-

Fig. 5. Amount of adaptation expressed as the ratio of the steady-state to the highest-peak amplitude plotted for both the N_1 and the N_2 components as a function of repetition rate at each stimulus intensity. As shown in Fig. 1b, the highest peak amplitude is the response to the first click in the train. As indicated by black to light grey graded symbol on the right, the steady-state adaptation is maximal for low values. Data are averaged from six animals and bars represent standard deviations.

Fig. 6. Resulting traces when normalized response curves obtained for N_1 (curves in right panel of Fig. 4) at given stimulus intensities and repetition rates were subtracted from the corresponding curves obtained for N_2 (curves in left panel of Fig. 4). Resulting curves are shown only for subtractions performed for responses obtained at 30, 50, and 70 dB SPL. Negative points mean that the normalized values obtained for N_2 were smaller (more adaptation) than those for N_1 at corresponding repetition rates and intensities. Note that as compared to Figs. 2–4 the ordinates axis has been expanded (0.15 maximal value instead of 1). Most differences between the two components are in the range of 5–10% (comparing the respective ratios of the steady-state to highest-peak amplitudes).

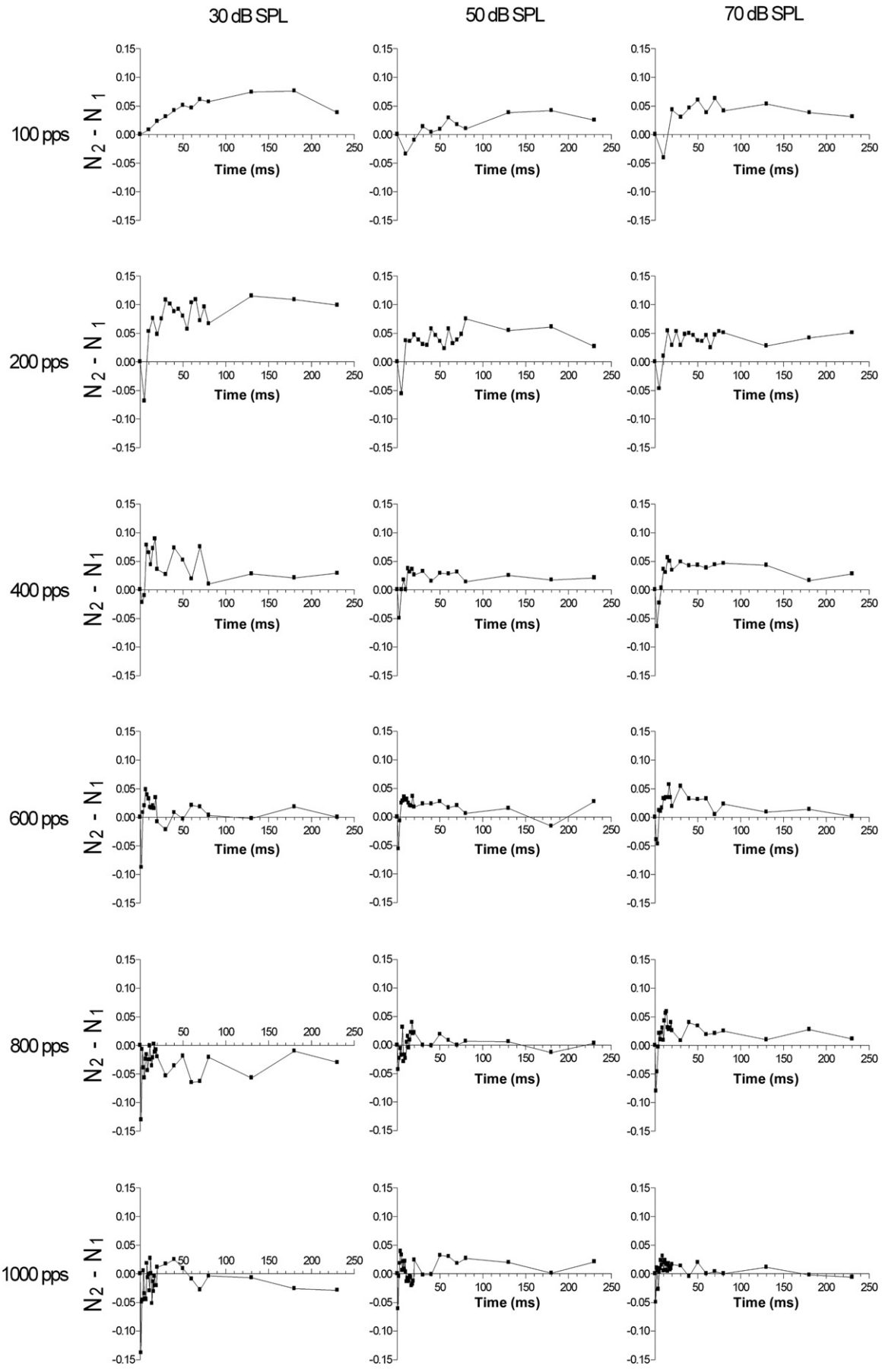


Table 2
Latency data in the rat for AN fibers (A) and CN units (B), derived from single-unit recordings

Study	Stimulus	Site of recording	Latency (ms)
(A)			
Møller, 1976	Amplitude-modulated tones	CN	1.1–1.7[a]
Møller, 1983	Amplitude-modulated tones	Not stated	0.5–1.8
FitzGerald et al., 2001	Clicks, 90 dB SPL	Anteroventral CN	1.5–3 (depending on CF)
Paolini et al., 2001	Clicks, 100 dB SPL	Anteroventral CN	1.4–2.7
(B)			
Møller, 1975	Rapid onset tone-bursts 42–102 dB SPL	CN	2.5–4.5 (depending on stimulus level)
Møller, 1976	Amplitude-modulated tones	CN	2.4–2.7[a] (depending on CF)
Møller, 1983	Amplitude-modulated tones	Not stated	2.0–3.0
Friauf and Ostwald, 1988	Tone pulses 30 dB above threshold	Ventral and intermediate acoustic striae	2.5–2.6[a] (primary-like units), 2.2[a] (on units)
FitzGerald et al., 2001	Clicks, 90 dB SPL	Anteroventral CN	2–4 (depending on CF)
Paolini et al., 2001	Clicks, 100 dB SPL	Anteroventral CN	1.7–4

[a] Averaged value.

tion of such pulsatile acoustic stimulation in modern cochlear and brainstem implants.

In a previous study, Loquet et al. (2004) showed that direct stimulation of the AN (thus by-passing the hair cell-nerve fiber synapse, as is the case in cochlear implants) with a train of electric pulses containing an adaptive component (intensity of individual pulses being varied over time) evoked realistic response envelopes in primary auditory neurons. The question now is as to what extent such a stimulus paradigm designed for stimulation of the AN could be applied directly to the brainstem, at the level of the CN, in the context of auditory brainstem implants. Such implants which directly stimulate the CN (e.g. Otto et al., 2002) may be necessary when damage is not restricted to the cochlea but involves also the AN as, for example, in type 2 neurofibromatosis which is often characterized by bilateral acoustic neurinoma (e.g. Schwartz et al., 2003). Our results suggest that the synapse between primary and secondary auditory neurons, as far as the VCN is concerned, does not profoundly modify the process of adaptation. Therefore, it seems that applying a stimulus paradigm as the one developed by Loquet et al. (2004) directly to the VCN may yield reasonable response envelopes in local neurons without the necessity of further modifications of the stimulus envelope making up for the second synapse by-passed. Of course, a definite verification of this issue must be empirical, applying electrical stimulation to the VCN of rats and recording the neural response, for example, in the superior olivary complex and/or the inferior colliculus. An important factor influencing the response behavior of secondary auditory neurons in addition to the mentioned synapse is their own refractory period; this issue shall be addressed below.

As mentioned in the results section, there are quantitative discrepancies between the adaptation patterns observed for N_1 and N_2 (Figs. 5 and 6). For instance, rapid adaptation was consistently somewhat more pronounced for N_2 than for N_1 (Fig. 6). A possible explanation for this enhanced adaptation in the VCN at the onset of repetitive stimulation is nerve cell refractoriness. Investigations in our laboratory showed that even when stimulating the AN electrically, the phenomenon of adaptation is still present (Haenggeli et al., 1998; Loquet et al., 2004). Since such electrical stimulation by-passes the hair cell-nerve fiber synapse, these studies suggest AN refractoriness to also be implicated in adaptation. Eggermont (1985) suggested AN refractoriness to be at the basis of rapid adaptation. Indeed, it seems quite plausible that the sometimes long relative refractory period of AN fibers (up to more than 5 ms in the guinea pig; Brown, 1994) affects response patterns to rapid pulsatile stimulation. Admitting that many neurons (of course depending on stimulus intensity) respond to the first stimulus in a train, subsequent refractoriness of most of these fibers would yield an initial rapid drop in response amplitude. If the refractory period of some VCN neurons was to last somewhat longer than that of AN fibers, this could explain why rapid adaptation was usually more pronounced for N_2.

Refractoriness must be assumed to also be of importance when answering the above question about the applicability of coding paradigms developed for the AN directly to the CN. If the refractory properties of primary and secondary auditory neurons were much different, the envelopes of the responses evoked by the same rapid pulsatile stimulation paradigm would probably diverge to. Based on the results of the present study, however, two statements can be made in this concern. On the one hand, as implied by the somewhat more pronounced rapid adaptation displayed by VCN neurons, their refractory period may indeed be somewhat longer (most certainly not shorter) than that of AN fibers. On the other hand, if this difference were very marked, one would expect more obvious discrepancies between the response envelopes displayed by primary and secondary auditory neurons.

Evidently, the variety of cell types in the dorsal CN is much wider than in the VCN, with onset, build-up and pauser units exhibiting very different response envelopes from that of primary auditory neurons. The influence of these neurons on the responses we registered from our electrode set in the VCN is probably minor because of the distance between them and the recording site. It is clear, that the above statement about the applicability of coding paradigms originally developed for stimulation of the AN directly to the brainstem is only valid for those cell types we could characterize in the present study, namely those located in the VCN. In as how much the sole stimulation of this ventral portion of the CN could restore hearing, especially speech perception, cannot be predicted with certainty. Obviously, an ideal brainstem implant would make use of more than one coding paradigm in order to stimulate the various parts, ultimately every distinct cell type, of the CN. The results of this study can only be applied to the VCN which, however, is larger by far than the dorsal CN. Further studies will be needed in order to refine stimulation of the cell types in the dorsal CN.

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