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Apical hair cells and hearing

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This study assessed the contribution of the apical hair cells to hearing. Guinea pigs, chinchillas and monkeys were behaviorally trained using positive reinforcement to respond to pure-tone stimuli. When a stable audiogram had been determined, each subject received one of three experimental treatments: ototoxic drug administration, low-frequency noise exposure, or the application of a cryoprobe to the bony wall of the cochlear apex. After post-treatment audiograms stabilized, subjects were euthanized and the percentage of hair cells remaining was assessed by light microscopy. Results indicate that a redundancy of encoding mechanisms exist in the mammalian cochlea for low-frequency stimuli. They also suggest that a very small percentage of apical hair cells are sufficient for some low-frequency hearing. Finally, data from this and other studies suggest that the low-frequency threshold shift caused by the loss of a certain percentage of apical hair cells is less pronounced than the high-frequency threshold shift caused by the loss of a comparable percentage of basal hair cells. These data agree with anatomical and electrophysiological evidence that functional as well as anatomical differences may exist between the apex and base of the cochlea.

Cochlear apex; Low-frequency hearing; Hair cells; High-pass auditory masking

Introduction

Anatomical, electrophysiological and behavioral data suggest that the apex and the base of the cochlea have distinct modes of processing auditory signals. Schuknecht and Neff (1952) used behaviorally conditioned cats to demonstrate that complete apical hair cell destruction resulted in a low-frequency hearing loss of 20–30 dB, while complete basal hair cell destruction produced a much more severe hearing loss. More recent behavioral experiments using guinea pigs, chinchillas, and monkeys (Stephenson et al., 1984; Clark and Bohne, 1986; Smith et al., 1987; Sommers et al., 1987) have generated similar findings.

Abundant anatomical differences between the base and the apex of the cochlea have been documented. These differences include changes in the width and thickness of the basilar membrane (Lim, 1980), the number, stiffness, and height of the stereocilia (Lim, 1980; Strelioff and Flock, 1984), the length of the outer hair cells (Bohne and Carr, 1985; Santi and Harrison, 1986), the density of myelinated nerve fibers (Bohne et al., 1982), the pattern of efferent (Ishi and Balogh, 1968; Robertson et al., 1987; Schuknecht et al., 1959; Spoendlin, 1979; Wright and Preston, 1973) and afferent (Spoendlin, 1979) nerve fiber projections, the sensitivity of the afferents to kainic acid (Pujol et al., 1985), the density of outer hair cell mitochondria (Hashimoto and Kimura, 1987), differences in the distribution of F-actin in the outer hair cells (Thorne et al., 1987), in the concentration of phosphoinositides (Niedzielski et al., 1988),

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and in the distribution of GABA in the medial efferent endings (Eyablin et al., 1988; Fex and Altschuler, 1984; Fex et al., 1986; Thompson et al., 1986). Further, Bohne et al. (1985) and Clark et al. (1987) have suggested that there are differences in the patterns of cellular destruction following low-and high-frequency noise exposures. Physiological differences include the observation that in the apex, outer hair cells produce well-defined DC responses (Dallos, 1985), whereas in the base they do not (Russell and Sellick, 1983).

In the present study, absolute threshold functions were determined from behaviorally-trained guinea pigs, chinchillas and monkeys before, during and after the production of an experimentally-induced sensorineural hearing loss. Behavioral and histological data were subsequently correlated. A primary objective was to produce very different patterns of apical hair cell retention by using several distinct experimental techniques; it was hoped that the correlation between the divergent patterns of hair cell destruction and the hearing losses associated with them would clarify the uncertain contribution of the apical hair cells to hearing.

Our findings indicate that equivalent patterns of hair cell destruction in the apex and in the base of the cochlea produce hearing losses which differ dramatically both in magnitude and abruptness, suggesting that functional differences may exist between the apex and the base of the cochlea.

Methods

Subjects

Eleven guinea pigs, eight chinchillas and six Old-World monkeys served as subjects in this study. All subjects were food-deprived to 80–90% of their incoming body weight, after which they gained weight throughout the experiment, reflecting normal developmental changes. Water was freely available in the home cages.

Guinea pigs (*Cavia porcellus*) received a total of 25 g of Purina guinea pig chow and/or 45 mg-Noyes Formula D food pellets daily, and fresh parsley weekly. Three of the eleven guinea pigs were monauralized prior to the beginning of behavioral testing by disarticulation of the right ossicular chain and surgical destruction of the right cochlea.

Chinchillas (*Chinchilla lanigera*) received a total of 10 g of Purina chinchilla chow and/or 45 mg-Noyes Formula N food pellets daily, supplemented with raisins, apple, and hay. They were individually housed in a room with a reversed light/dark cycle. All chinchillas were monauralized prior to the beginning of behavioral testing by disarticulation of the right ossicular chain and cryoprobe destruction of the entire right cochlea.

Three of the six monkey subjects were *Erythrocebus patas*, and three were *Macaca nemestrina*. They were fed a diet which consisted of Purina monkey chow, Bioserv primate banana-flavored pellets, and fresh fruit.

Apparatus

Subjects were tested in IAC double-walled sound-attenuating chambers. Monkeys were seated in a primate restraint chair; guinea pigs and chinchillas were placed in a wire mesh testing cage located in an IAC chamber. The testing apparatus for each species included a feeder, a response manipulandum, a light, and a sound delivery system consisting of a speaker for the rodents and earphones for the monkeys (guinea pig, Prosen et al., 1981; chinchilla, Smith et al., 1987; and primate, Moody et al., 1976). The behavioral procedure for the guinea pigs was controlled by solid state logic circuits (BRS-LVE Digi-bits), and for the chinchillas and monkeys by a Digital Corporation PDP-8E computer.

Stimuli

The guinea pig pure-tone auditory stimulus generating apparatus has been described elsewhere (Prosen et al., 1978). For those guinea pigs from which masking data were collected, the masker originated from a General Radio Company Random Noise Generator (model 1381), to an Allison Laboratories variable filter (model AL-2ABR), a 1/3-octave center frequency equalizer, a Crown amplifier (DC 300A), and finally delivered by an Audio Dynamics Speaker (model XT-6). The chinchilla pure tone stimulus generating apparatus, equipment used during masking experiments,

and sound field calibration procedures have been described by Smith et al. (1987). Pure-tone stimulus generation and calibration procedures for the monkey have been described by Moody et al. (1976).

Acoustic exposures for guinea pigs and monkeys were carried out in an IAC sound booth which was modified to increase its reverberance. The noise was produced by a General Radio random noise generator (model 1381), filtered by an Allison Laboratories variable filter (model 2BR), passed through a 1/3-octave center frequency equalizer, and amplified by a McIntosh power amplifier (model MC2105). The noise was delivered to the animals via one (guinea pig) or two (monkey) Altec 'Voice-Of-The-Theater' speaker systems, which were mounted on the ceiling and directed at the animals being exposed.

The sound field spectrum of the noise, whether used during masking or exposure, was calibrated with a Hewlett-Packard wave analyzer (model 3590A) and a 1/2-inch condenser microphone. Overall sound levels were measured with a sound level meter (C weighting). The 0.71 kHz cutoff high-pass masking noise described below had a flat spectrum from 0.71 to 12.0 kHz, with a 10-dB decrease from 12.0 to 22.0 kHz.

Procedure

Pre-treatment testing

The training and testing of each animal species were conducted according to a similar behavioral protocol and have been described in detail elsewhere (guinea pig: Prosen et al., 1978; Prosen and Stebbins, 1980; chinchilla: Smith et al., 1987; monkey: Moody et al., 1976). Guinea pig thresholds were determined by the method of constant stimuli, while chinchilla and monkey thresholds were determined by a tracking procedure. Baseline data were considered stable when 4 out of 5 successive thresholds at each test frequency were within 10 dB.

After the collection of stable baseline data, three of the guinea pigs and five of the chinchillas were subjects in a high-pass (0.71 kHz cutoff) masking experiment. Absolute thresholds were evaluated in the presence of the masker, which was adjusted in level to produce a 10–20 dB increase in threshold at frequencies of 0.71 kHz and higher. Masking data were judged stable by the criteria described above. The masking experiment was conducted to evaluate the hypothesis that in instances of apical hair cell destruction with basal hair cell retention, hair cells located basal to the apical destruction detect low-frequency tones normally detected by the apical hair cells. In both the normal and the damaged ear, a high-pass masker should increase the thresholds of frequencies within the pass band. In the ear with apical hair cell destruction, if more basally-located cells detected low-frequency signals, thresholds for the low frequencies should be elevated, too.

Experimental treatment and post-treatment testing

After stable baseline data were gathered, the experimental treatment began.

All guinea pigs were exposed to either a pure tone or noise. Two subjects (GP1 and GP2) were exposed to a 0.25-kHz octave band noise (OBN) at 115 dB SPL, 22 h/day for 7 consecutive days. Two other subjects (GP12 and GP13) were exposed to a 0.5-kHz OBN at 110 dB SPL, 22 h/day for 13 consecutive days. Four subjects (GP3, GP4, GP21, and GP22) were exposed to a 0.5-kHz OBN at 120 dB SPL, 22 h/day for 7 consecutive days. The remaining three subjects (GP32, GP38, and GP41) were exposed to a 0.5-kHz pure tone at 120 dB SPL, 22 h/day, for 7 consecutive days. Thresholds were evaluated at the conclusion of each daily exposure period.

All chinchillas had a cryoprobe applied to the left cochlea. This procedure has been described in detail elsewhere (Brown and Nuttall, 1987; Smith et al., 1987). Briefly, while each subject was under general anesthesia, the left bulla was opened and the tip of a liquid-nitrogen-cooled cryoprobe was placed on the apex. For six of the subjects (CH15, CH83, CH84, CH94, CH98, and CH118), the probe remained in place for 1.5 min; it was then removed for 3 min, and reapplied for an additional 1.5 min. CH34 had cryoprobe placement durations of 2 and 3 min, with a 4 min interval between placements. CH47 had one 3-min cryoprobe application. Behavioral testing of the chinchillas resumed within 2–3 days after surgery.

Two monkeys (M54 and M49) were exposed to

a 0.5-kHz OBN at 120 dB, 8 h/day for 20 days. Exposures were not conducted on weekends. Hearing in both ears was evaluated at the conclusion of the daily exposure period.

The remaining four monkeys were treated with an aminoglycosidic antibiotics. M44 and M62, both patas monkeys, were treated with dihydrostreptomycin (DHSM) 100 mg/kg/day intramuscularly; M44 received DHSM for 110 days, and M62 for 75 days. M91, the third patas monkey, received 20 mg/kg/day DHSM for 100 days. Finally, M21 received neomycin (NM) 50 mg/kg/day intramuscularly for 15 days. Threshold testing continued throughout the drugging procedure.

Hearing of all subjects was assessed until the threshold shift stabilized according to the criterion described above. Thresholds of the guinea pigs (three) and the chinchillas (five) were then determined in the presence of the high-pass masker. Data collection from these subjects was terminated when the thresholds met the pre-determined stability criterion.

Histology

At the conclusion of behavioral testing, guinea pigs and chinchillas were heavily anesthetized with ketamine-rompun and decapitated. Temporal bones were quickly removed, and the bulla and the round and oval windows exposed and opened. Fixative was then gently perfused through the round window. Fixative was either 2.5% glutaraldehyde or 2.5% glutaraldehyde and 2% paraformaldehyde in phosphate buffer. After 1 hour of fixation, cochleae were rinsed in buffer. In guinea pigs, but not chinchillas, this was followed by an intrascalar perfusion of 1% OsO4 and a second series of rinses. Cochleae were subsequently dehydrated through 70% alcohol. The bony shell was then removed, and stria and segments of the cochlear spiral recovered in complete turns. These surface preparations were then flat embedded in medcast-araldite in slide molds.

At the conclusion of the monkey behavioral testing, subjects were heavily anesthetized with sodium pentobarbital, and the membranous labyrinth was fixed and stained in vivo by perilymphatic perfusion of 1% OsO4 solution (Zetterqvist). Cochlear tissues were prepared by microdissection as described by Hawkins and Johnsson (1976).

The surface preparations were examined with a light microscope with phase contrast optics. The number of missing hair cells was assessed in all segments of the entire cochlear spiral. Cytocochleograms were constructed from the surface preparations, in which the percentage of inner and outer hair cells remaining was plotted as a function of the percent distance from the apex of the cochlea. Cells were counted as present if either the stereocilia or the cell nucleus could be visualized. No attempt was made to assess the degree of possible cellular damage to surviving cells. Because hearing in chinchillas and monkeys was assessed monaurally (chinchillas were monauralized and monkeys were tested with earphones), cytocochleograms from these subjects were correlated with the behavioral data from the ear used during testing. In those guinea pigs which were not monauralized prior to behavioral testing, the cytocochleogram from each subject with the least amount of cellular damage was correlated with the behavioral threshold shift data, under the assumption that the animal used its best ear while performing the psychophysical task.

Results

Data from the subjects in this experiment are grouped on the basis of the pattern of hair cell loss following the experimental treatment, as seen in Table 1. Group 1 subjects had partial loss of apical hair cells and good retention of basal hair cells. Group 2 subjects had complete loss of apical hair cells with good retention of basal hair cells. Group 3 subjects had complete apical hair cell destruction and partial loss of basal cells. Group 4 subjects had some apical hair cells remaining but no basal cells. This classification scheme potentially ignores hair cells from the middle region of the cochlea; when these cells appeared normal, their role in detection is considered. Because of the large number of subjects in this study, representative data from each group were selected and are described below, and deviations from these representative results are noted.

TABLE I

HAIR CELL CONDITION AND HEARING LOSS IN GROUPS 1-4

Group number	Apical hair cell condition	Basal hair cell condition	Hearing loss
1	partial to substantial loss	No loss	0–25 dB low-frequency loss
2	Complete loss	No loss	0–25 dB low-frequency loss
3	Complete loss	Partial loss	40–60 dB loss at all frequencies
4	Substantial loss	Complete loss	20–40 dB low-frequency loss; 60–100 dB mid-frequency loss; no remaining high-frequency hearing

Group 1 (Partial apical loss, good basal retention)

Eleven of the Group 1 subjects were noise-exposed guinea pigs, two were noise-exposed monkeys, and one was a cryoprobe-treated chinchilla. The data from the monkeys (M49 and M54) were first reported by Moody et al. (1978).

GP1 was exposed to a 0.25-kHz OBN, 115 dB SPL, 22h/day, for 7 days. The upper half of Fig. 1 shows the cytocochleogram for the left ear of GP1, while the lower half of this figure depicts the threshold shift. In the apical 25% of GP1's left cochlea, 10–90% of OHCs were absent, while IHCs here were well-retained. Corresponding to this pattern of hair cell loss, no measurable threshold shift was noted at any frequency.

GP13 was exposed to a 0.5-kHz OBN, 110 dB SPL, 22 h/day, for 13 days. In the apical 40% of the right cochlea, approximately 50% of the OHCs were absent, while IHCs here were retained reasonably well, as seen in Fig. 2. Low-frequency thresholds were shifted by 10 dB at most. Two additional Group 1 guinea pigs were exposed to a 0.5 kHz OBN, one at 110 and one at 115 dB SPL: both animals had approximately 50% OHC loss in the apical 30% of the cochlea, with no hearing loss at any frequency.

GP41 was exposed to a 0.5-kHz pure tone at 120 dB, with the expectation of producing more hair cell destruction than had been produced in subjects exposed to lower levels. As seen in Fig. 3, with 10–60% of the OHCs missing in the apical 15% of the cochlea, thresholds below 0.25 kHz shifted by 10 dB at most, whereas the loss at 16.0 and 32.0 kHz was 15 to 20 dB, and at 1.0 kHz it was 30 dB. In general, subjects exposed to this higher level (120 dB) suffered greater high-frequency hearing loss than would have been predicted from the cytocochleogram. Ten additional sets of cytocochleograms and audiograms were collected from 6 guinea pigs and 2 monkeys which were exposed to sound at 120 dB SPL, the guinea pigs for 7 days, 22 h/day, and the monkeys for 20 days, 8 h/day. In eight of these sets of data, some high-frequency hearing loss was noted, unaccompanied by any substantial basal hair cell loss. In none of these sets of data did the hearing loss at frequencies below 1.0 kHz exceed 20 dB, although apical hair cell loss ranged from 20–90 %.

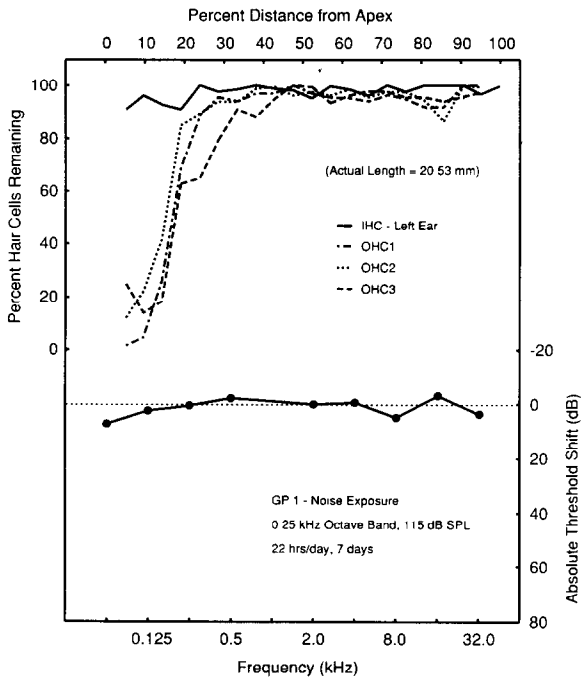

Fig. 1. Left ear cytocochleogram and absolute threshold shift function of GP1, a guinea pig exposed to a 0.25 KHz OBN at 115 dB SPL (C scale), 22 h/day, for 7 days. Frequency and distance axes are aligned as described by Prosen et al. (1978).

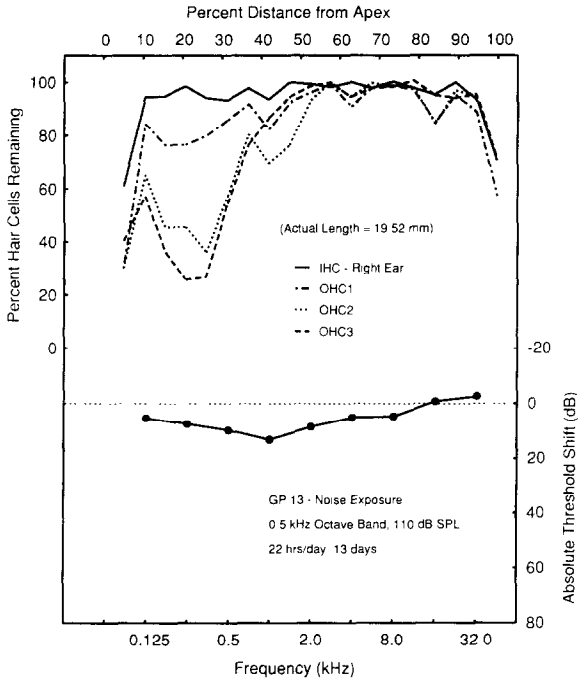

Fig. 2. Right ear cytocochleogram and absolute threshold shift function of GP13, a guinea pig exposed to a 0.5 kHz OBN at 110 dB SPL (C scale), 22 h/day, for 13 days. Frequency and distance axes are aligned as described by Prosen et al. (1978).

It could be argued that in the presence of apical hair cell destruction, mid-and basal-turn hair cells respond to low-frequency stimuli which, in the normal ear, are responded to by apical hair cells. To evaluate this possibility, a high-pass (0.71 kHz and above) masking noise was introduced into the testing environment of GP41. Thresholds measured in the presence of this masker are displayed in Fig. 3. While thresholds for frequencies of 1.0 kHz and above increased 10–20 dB in the presence of the masker, thresholds for lower frequencies were unchanged. Nearly identical masking data were collected from a second sound-exposed guinea pig, while masking data from a third guinea pig demonstrated a 20-dB hearing loss for mid-range frequencies in the presence of the high-pass masker and a more modest 5-dB hearing loss for low frequencies. These data suggest that in the presence of partial apical OHC loss, low-frequency stimuli may be responded to either by the remaining apically-located hair cells, or by adjacent undamaged hair cells.

The final Group 1 subject was a cryoprobe-lesioned chinchilla. Approximately 70% of the OHCs and 10–80% of the IHCs in the apical half of the cochlea were destroyed. While the apical damage was more extensive in this subject than in the other Group 1 subjects, the hearing loss was similar in magnitude: the maximum threshold shift noted at any frequency was 15 dB.

Group 2 (Complete apical loss, good basal retention)

All four subjects in Group 2 were chinchillas that had a cryoprobe applied to the left cochlear apex, in the expectation that more substantial apical hair cell loss would be produced by this procedure than by sound-exposure. In fact, all of the subjects in this group showed considerable apical hair cell destruction. Data from two of the

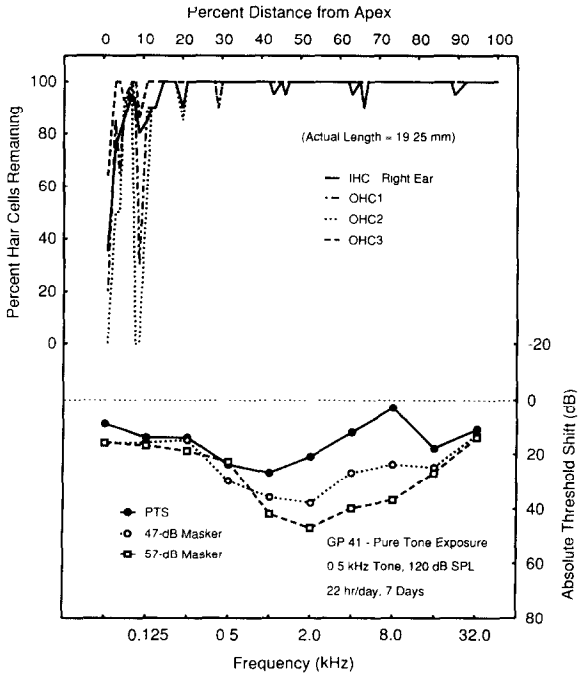

Fig. 3. Right ear cytocochleogram and absolute threshold shift functions of GP41, a guinea pig exposed to a 0.5 kHz pure tone at 120 dB SPL (C scale), 22 h/day, for 7 days. PTS data refer to the threshold shift measured in the absence of a masker, while 47- and 57-dB masker data refer to the threshold shift measured in the presence of a 0.71 kHz high-pass masker set at 47 and 57 dB SPL (C scale). Frequency and distance axes are aligned as described by Prosen et al. (1978).

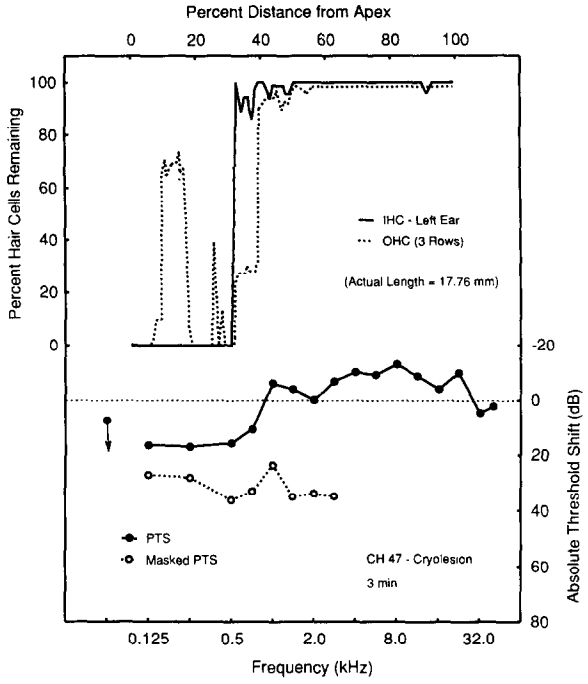

Fig. 4. Left ear cytocochleogram and absolute threshold shift functions of CH47, a chinchilla which had a cryoprobe applied to the apex of the bony wall of the cochlea once for 3 min. PTS data refer to the threshold shift measured in the absence of a masker, while masker data refer to the threshold shift measured in the presence of a 0.71 kHz high-pass masker. The downward arrow indicates that the extent of the threshold shift could not be determined at the corresponding frequency. Frequency and distance axes are aligned according to the method of Eldredge et al. (1981). (Data from Smith et al. 1987).

Group 2 subjects (CH47 and CH94) have been reported by Smith et al. (1987).

Fig. 4 shows the left ear cytocochleogram and threshold shift function of CH47. All of the IHCs, and most of the OHCs, were missing in the apical 30% of the cochlea; low-frequency thresholds shifted by at most 15 dB, while high-frequency thresholds were unchanged. Downward arrows in the lower half of this and subsequent figures indicate that the extent of the threshold shift could not be determined at the corresponding frequency. Threshold shift was sometimes difficult to measure at very high and very low frequencies because the subjects' normal absolute thresholds were high at these frequencies. The cytocochleogram and threshold shift function of CH84, shown in Fig. 5, indicate that in the absence of all of the hair cells in the apical 30% of the cochlea, thresholds shifted by at most 20 dB. Data from CH94, seen in Fig. 6, corroborate the findings from CH47 and CH84; in the absence of nearly all of the apical hair cells, low-frequency thresholds shifted by at most 15 dB. The cytocochleogram and threshold shift function of CH83, the fourth Group 2 subject, indicated that in the absence of all hair cells in the apical 35% of the cochlea, low-frequency thresholds shifted at most by 20 dB, while basal hair cells were normal and high-frequency thresholds were unchanged.

High-pass masking data were collected from all of these subjects. Data from CH47 and CH84 demonstrate that in the presence of the masker, thresholds at all frequencies were elevated, suggesting that when apical IHCs are completely

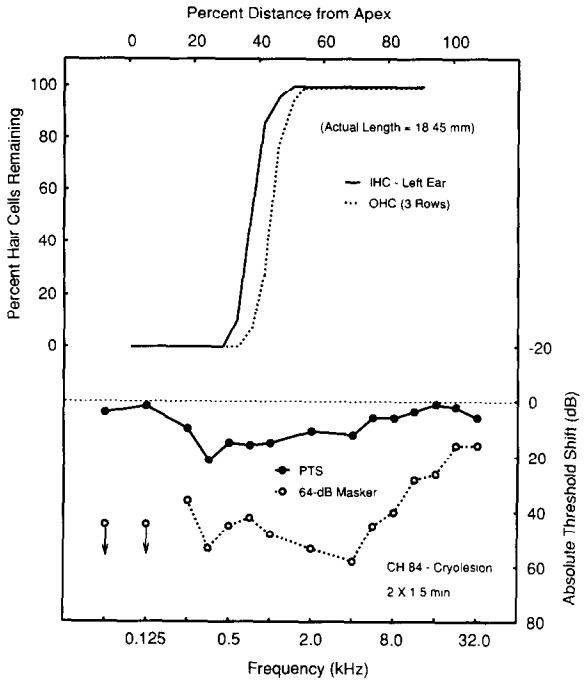

Fig. 5. Left ear cytocochleogram and absolute threshold shift functions of CH84, a chinchilla which had a cryoprobe applied to the apex of the bony wall of the cochlea twice, with application durations of 1.5 min and an interapplication interval of 3 min. PTS data refer to the threshold shift measured in the absence of a masker, while masker data refer to the threshold shift measured in the presence of a 0.71 kHz high-pass masker set to 64 dB SPL (C scale). Downward arrows as in Fig. 4. Frequency and distance axes are aligned according to the method of Eldredge et al. (1981).

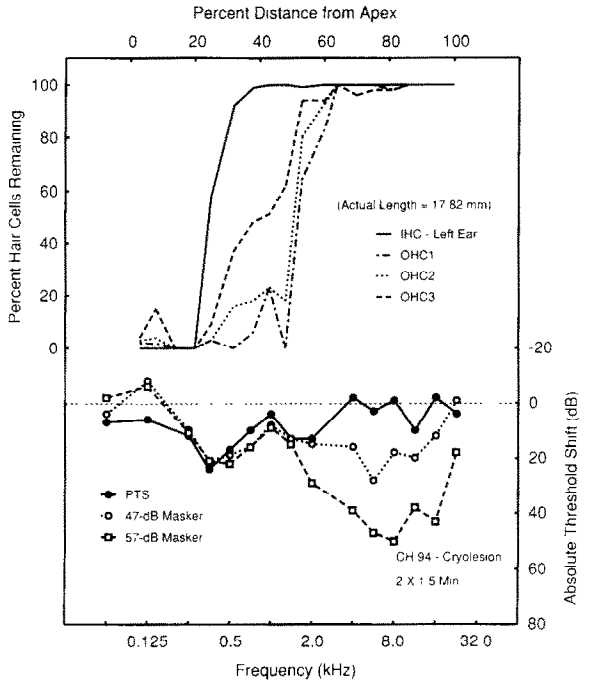

Fig. 6. Left ear cytocochleogram and absolute threshold shift functions of CH94, a chinchilla which had a cryoprobe applied to the apex of the bony wall of the cochlea twice, with applications durations of 1.5 min and an interapplication interval of 3 min. PTS data refer to the threshold shift measured in the absence of a masker, while 47- and 57-dB data refer to the threshold shift measured in the presence of a 0.71 kHz high-pass masker set to 47 and 57 dB SPL (C scale). Frequency and distance axes are aligned according to the method of Eldredge et al. (1981).

destroyed, undamaged mid- and basal-turn hair cells detect low-frequency stimuli. Masking data from CH94 appear to contradict this statement: in the presence of the high-pass masker, only high-frequency thresholds were elevated. However, close attention to Fig. 6 suggests that some undamaged IHCs remained which were located in an area of the cochlea that encoded frequencies below the low-frequency cutoff of the masker. Perhaps the response of the non-apical cells to low-frequency stimuli is only revealed when all apical IHCs have been destroyed. That is, basal cells may respond to high-level low-frequency stimulation at all times in the normal ear, but they may mediate low frequency hearing only when apical regions are destroyed.

Group 3 (Complete apical loss, partial basal loss)

The three subjects in this group, with complete loss of apical and partial loss of basal hair cells, were monauralized chinchillas whose remaining (left) ear was treated with a cryoprobe. Data from CH34 were reported by Smith et al. (1987). Fig. 7 shows the left ear cytocochleogram and threshold shift function of CH34. OHCs were destroyed throughout the cochlea, while IHCs were present, except in the apical 20% of the cochlea. Thresholds shifted at all frequencies by 40–60 dB, except at 22.4 kHz, where the shift was 22 dB.

Fig. 8 shows the left ear cytocochleogram and permanent threshold shift function for CH98. OHCs were present only in the basal-most 10% of the cochlea. IHCs were entirely absent from the upper 20%, and throughout most of the apical half, but were mostly retained in the basal half of the cochlea (60–90%). Thresholds, however, in-

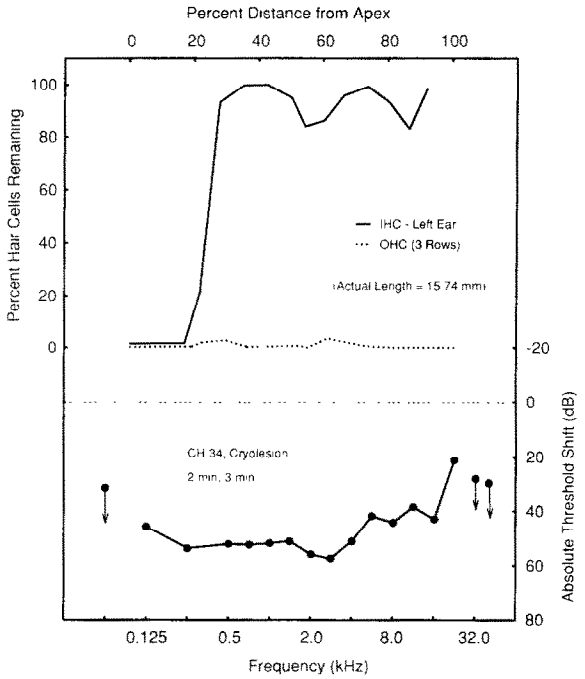

Fig. 7. Left ear cytocochleogram and absolute threshold shift function of CH34, a chinchilla which had a cryoprobe applied to the apex of the bony wall of the cochlea twice, with application durations of 2.0 and 3.0 min and an interapplication interval of 4 min. Downward arrows as in Fig. 4. Frequency and distance axes are aligned according to the method of Eldredge et al. (1981). (Data from Smith et al., 1987).

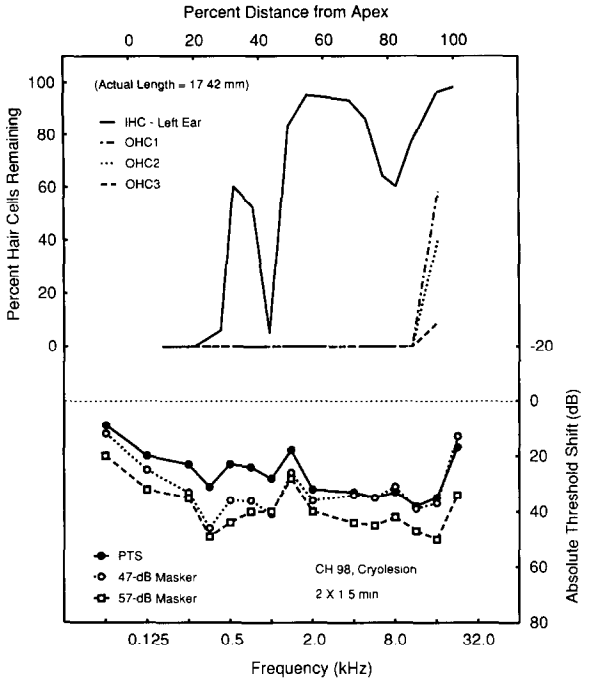

Fig. 8. Left ear cytocochleogram and absolute threshold shift functions of CH98, a chinchilla which had a cryoprobe applied to the apex of the bony wall of the cochlea twice, with application durations of 1.5 min and an interapplication interval of 3 min. PTS data refer to the threshold shift measured in the absence of a masker, while 47- and 57-dB masker data refer to the threshold shift measured in the presence of a 0.71 kHz high-pass masker set to 47 and 57 dB SPL (C scale). Frequency and distance axes are aligned according to the method of Eldredge et al. (1981).

creased at all frequencies by 20–40 dB; the threshold shift for 1.0 kHz and below was slightly less (23 dB) than that for 1.0–16.0 kHz (30 dB). This finding of a smaller shift for low-frequencies than for high-frequencies was duplicated in the data of CH118, the third Group 4 subject, while the pattern of hair cell loss was similar for CH98 and CH118. High-pass masking data from CH98, seen in Fig. 8, confirm the hypothesis that undamaged basal cells responded to low-frequency stimuli; in the presence of the 57-dB masker, thresholds at all frequencies were elevated by 10–20 dB.

Throughout this experiment, a substantial (greater than 30 dB) low-frequency threshold shift was produced only when both apical and basal hair cells were damaged. This finding, in conjunction with the high-pass masking data, suggests that low-frequency hearing can be mediated by basal hair cells.

Group 4 (Partial apical loss, complete basal loss)

The four subjects in this group were monkeys treated with aminoglycosides. Data from three of these monkeys (M44, M62, and M91) were described by Hawkins et al. (1977), while data from M21 were detailed by Stebbins et al. (1969). The right ear cytocochleogram and permanent threshold shift function of M62, treated with 100 mg/kg/day DHSM for 75 days, are seen in Fig. 9. Less than 20% of IHCs or OHCs were present in the apical 20% of the cochlea, while no hair cells were present in the remaining 80% of the cochlea. Hearing was restricted to frequencies of 0.5 kHz and below.

The right ear cytocochleogram and permanent threshold shift function of M91, a patas monkey treated with 20 mg/kg/day DHSM for 100 days, are depicted in Fig. 10. Zero to forty percent of

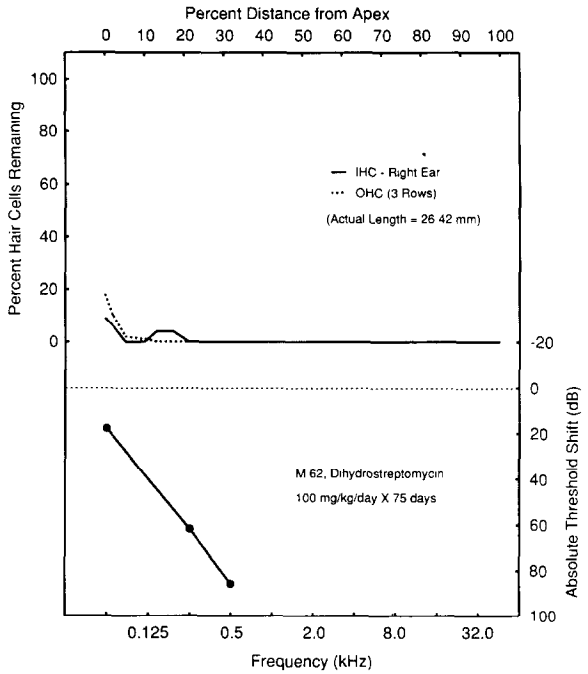

Fig. 9. Right ear cytocochleogram and absolute threshold shift function of M62, a monkey (Macaca nemestrina) treated with 100 mg/kg/day dihydrostreptomycin for 75 days. Frequency and distance axes are aligned as described by Stebbins et al. (1987). (Data from Hawkins et al., 1977).

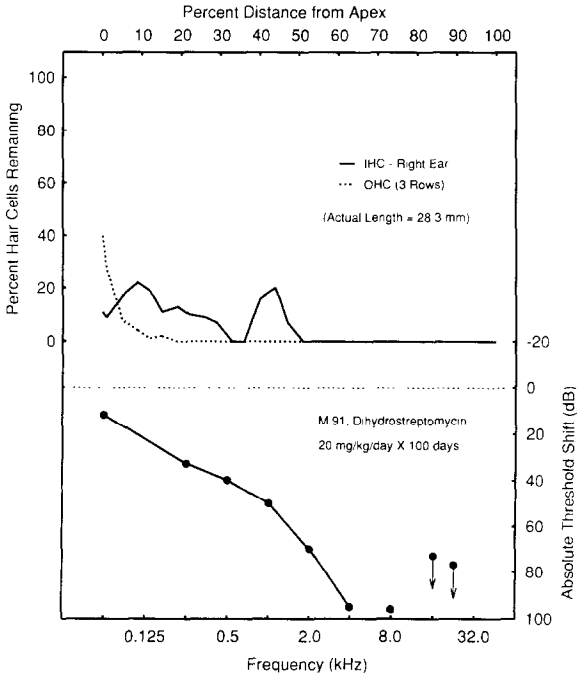

Fig. 10. Right ear cytocochleogram and absolute threshold shift function of M91, a monkey (Erythrocebus patas) treated with 20 mg/kg/day dihydrostreptomycin for 100 days. Downward arrows as in Fig. 4. Frequency and distance axes are aligned as described by Stebbins et al. (1987).

OHCs were present in the apical 40% of the cochlea, while 0–25% of IHCs remained in the apical 50% of the cochlea. No hair cells were present in the basal half of the cochlea. Corresponding to this pattern of remaining hair cells, M91 responded to stimuli from 0.063 to 4.0 kHz after drug treatment. The data suggest that in the presence of massive apical and complete basal hair cell loss, low-frequency thresholds may shift by only 20–40 dB.

Five additional sets of cytocochleograms and audiograms were available from the Group 4 subjects. Of these, one set was remarkably similar to data from M62, with hearing limited to frequencies 0.5 kHz and below and hair cells remaining only in the apical 10% of the cochlea. The remaining four demonstrated hearing up to 4.0 kHz (3 animals) or 8.0 kHz (1 animal); thresholds at these high frequencies had shifted by 60–90 dB. The majority of remaining hair cells in all cytocochleograms was limited to the apical 25% of the cochlea.

Discussion

The intent of this study was to evaluate the hearing which remained following the differential destruction of apical hair cells. The variety of lesioning techniques employed produced different patterns of hair cell destruction which were categorized into four groups.

Data from Group 1 subjects indicate that with 50% apical OHC destruction, thresholds increased by at most 10 dB. These data are in contrast to data describing threshold shifts following damage in the basal cochlea. Ylikoski (1974) reported that in the guinea pig, after destruction of row 1 basal OHCs, thresholds shifted by 18 dB, of row 2 OHCs, by 38 dB; and all 3 rows of OHCs, by 42 dB. Similarly, with substantial basal OHC loss and good basal IHC retention, Hawkins et al. (1977), Prosen et al. (1978), and Stebbins et al. (1987) reported a 40–60 dB high-frequency hearing loss.

Masking data from the subjects with partial apical hair cell loss suggested that the remaining apical cells can detect low-frequency signals at low levels, concurring with the finding of Clark and Bohne (1986) that a full complement of apical hair cells is not necessary for nearly normal threshold detection of low frequency stimuli. The basal cochlea does not behave in this fashion; partial hair cell loss is always accompanied by a measurable hearing loss.

When the level of the noise-exposure was increased to 120 dB for the guinea pigs in Group 1, hearing often changed at middle and high frequencies in the absence of a corresponding hair cell loss. This pattern of substantial hearing loss unaccompanied by hair cell destruction has been described in studies using high levels of noise (Salvi et al., 1982; Shaddock and Borszcz, 1986; Borg, 1987; and Sinex et al., 1987). Liberman and Beil (1987) suggested that stereocilia alterations observed with the light microscope were the best indicator, in addition to cell death, of the threshold elevation measured in single auditory nerve fibers. Shaddock and Borszcz (1986) described subtle changes in OHCs located in the shoulder of a noise-induced lesion 3 months post-exposure; presumably, these cells, which had intact stereocilia, would have been counted present when using the

light microscope to construct cytocochleograms. Clearly, light microscopic examination focussed on the presence or absence of the hair cell stereocilia or nucleus does not reveal the subtleties of hair cell damage that can be caused by high level noise exposure.

Data from Group 2 subjects suggest that with complete apical hair cell destruction, thresholds shifted by less than 30 dB, concurring with data from earlier studies (Schuknecht and Neff, 1952; Butler and Albrite, 1956). These data differ from the 80-dB or greater threshold shift resulting from complete basal hair cell destruction (Ylikoski, 1974; Hawkins et al., 1977). Masking data from Group 2 subjects suggest that with complete apical hair cell loss, undamaged mid- and basal-turn receptor cells detect low-frequency stimuli. Physiological single-unit eighth-nerve tuning curves recorded from mid- and basal-turn fibers have long low-frequency tails (Kiang et al, 1965); presumably information from this part of the tuning curve is used to detect low-frequency signals in the absence of the apical hair cells.

Both the post-drug threshold shift and masking functions from subjects in Group 3 demonstrate that basal hair cells can mediate low-frequency hearing. In two of the three subjects from this group, the low-frequency threshold shift was less than the high-frequency threshold shift. Apical hair cells were completely destroyed in these subjects. Hence the remaining basal hair cells encoded low-frequency signals with a smaller threshold shift than they encoded high-frequency signals. Kiang et al. (1976) and Liberman and Dodds (1984) reported hypersensitive low-frequency tails of tuning curves measured electrophysiologically from auditory-nerve fibers of cats exposed to noise or treated with aminoglycosides. Perhaps physiological tuning curve tail hypersensitivity was the basis for the finding in the present study that high-frequency thresholds were sometimes elevated more than low-frequency thresholds in cases of primary apical receptor cell damage.

Addition of a 47-dB masker to the testing environment of CH98 elevated thresholds at most frequencies, but a 10-dB increase in masker level to 57-dB did not produce a corresponding 10-dB increase in all low-frequency thresholds. Turner et al. (1983) described similar results from a high-pass masking experiment involving humans with low-frequency sensorineural hearing loss. These authors suggested that when low-frequency tones are increased in level, remaining, possibly damaged cells may begin to contribute to the response, producing a non-linear relationship between masker level increase and threshold increase. While apical OHC destruction was complete in CH98, the remaining IHCs located 20–40% from the apex may have attenuated the increase in threshold with increasing masker level.

While multiple mechanisms exist for detecting low frequencies, the discrimination between low frequency signals may be impaired following apical receptor cell damage. Several investigators (Zurek and Formby, 1981; Tyler et al., 1983; Clark and Bohne, 1986; Nelson and Freyman, 1986; Prosen et al., 1989) have suggested that frequency discrimination at low frequencies may be impaired in the presence of little or no low frequency hearing loss, while Fitzgibbons and Wightman (1982) noted that low-frequency gap-detection thresholds increased while low frequency absolute thresholds were normal.

When only apical hair cells remained, as noted in the drug-treated monkeys, hearing was limited to the low- and mid-range frequencies. These data are noteworthy in that the 'place' principle of hearing is based primarily on data from studies which created a basal hair cell loss in experimental animals. A second experiment which supports the 'place' principle but is not based on basal hair cell loss was reported by Liberman (1982). In this study, auditory nerve fibers with a known characteristic frequency were labeled and traced back to their place of innervation; fibers with characteristic frequencies of 100–200 Hz were localized in the apical end of the cochlea. The data are also of interest because they suggest that apical hair cells may respond to frequencies up to 4.0 kHz at levels 65–95 dB above pre-drug thresholds. Given the uncertainty associated with cochlear frequency maps, it is possible that the remaining hair cells of M62 and M91 were responsible for the hearing which these subjects reported. Cazals and colleagues (Aran et al., 1979; Cazals et al., 1979, 1980, 1982, 1983) treated guinea pigs with the ototoxic aminoglycoside amikacin and produced lesions which were similar to those of M62 and

M91. They subsequently recorded acoustically-evoked, high-threshold neural responses from the round window, which they interpreted as being of saccular rather than of cochlear origin. The high-threshold mid-range frequency behavioral data of M91 are reminiscent of data of Cazals et al. While all of M91's responses to acoustic stimuli may have been mediated by cochlear hair cells, it is possible that the responses were of vestibular rather than of cochlear origin.

While basal OHCs are more susceptible to damage from ototoxic drugs than are basal IHCs, a reverse pattern of hair cell susceptibility to drugs was noted in this experiment in the apex. This apparent paradox was described earlier by Lim (1976) in drug-treated guinea pigs. Dallos (1985) suggested that apical OHCs may play some role in transduction, while transduction in the base is traditionally thought to be carried out by IHCs. The finding that apical OHCs responded to ototoxic drug treatment like basal IHCs may be consistent with the idea that apical OHCs and basal IHCs share some similarities.

Kidd and Mason (1982) suggested that while the incidence of human apical hair cell loss may be underestimated because the normal base can compensate for apical destruction, low-frequency hearing loss of sensorineural origin has been documented in humans (see also Iinuma et al., 1967; Vanderbilt University Hereditary Deafness Study Group, 1968; Konigsmark et al., 1971; Long and Cullen, 1988). Indeed, apical hair cell loss is a known concomitant of aging in mammals (Coleman, 1976; Bhattacharyya and Dayal, 1985; Hawkins and Johnsson, 1985; Keithley and Feldman, 1982), although its effects may be minor compared to damage from other factors, like noise or drugs (Bhattacharyya and Dayal, 1985).

Data from this study suggest that fundamental differences exist between apical and basal hair cells. An alternative explanation is based on the known asymmetry of the auditory-nerve tuning curves, where high-frequency slopes are steeper than low-frequency slopes. Further, as noted above, the tails of tuning curves are sometimes hypersensitive in pathological ears. These phenomena could mask the effects of an apical receptor cell loss by the recruitment of higher frequency fibers at somewhat higher sound pressure levels, thereby accounting for the near-normal low-frequency hearing evident in some of the subjects. Future research using non-human subjects and more complex auditory psychophysical tasks should be useful in revealing the contribution of the cochlear apex to hearing in the normal ear. Especially important in this regard will be the role of the apical hair cells in the discrimination of suprathreshold low-frequency stimuli.

Summary

1. When up to 50% of the apical hair cells were missing, and mid- and basal-turn cells were well-preserved, low-frequency thresholds rose by at most 10 dB. High-pass masking data suggested that the remaining apical hair cells detected the low-frequency stimuli. Hence, for low-frequency thresholds, the apical OHCs are relatively unimportant. For suprathreshold responses, however, they may well be necessary.

2. When apical hair cell destruction was complete, and mid- and basal-turn cells were well-retained, low-frequency thresholds increased by at most 30 dB. High-pass masking data in animals with this pattern of cochlear pathology suggest that undamaged mid- and basal-turn cells responded to low-frequency stimuli.

3. With complete apical, and partial basal hair cell loss, thresholds shifted at all frequencies. In animals with this form of cochlear pathology, thresholds at low-frequencies sometimes shifted less than thresholds at high-frequencies. Since only basal cells remained, these cells, tuned to high-frequencies, responded at lower energy levels to low-frequency signals than to high-frequency signals.

4. When only a small percentage of apical hair cells were present, hearing was restricted to low-frequencies. These remaining apical hair cells detected low-frequency stimuli with a 20–50 dB threshold shift at the lowest frequencies.

5. The low-frequency hearing loss that follows the destruction of a given percentage of apical hair cells is smaller than the high-frequency hearing loss that follows the destruction of an equal percentage of basal hair cells.

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