staining.[44] In our present study the TZ was more clearly observed with anti-GFAP immunostaining because astrocytes are found only in the CNS portion of the auditory nerve (Fig. 2).

At the fundus of the IAC, multiple tiny osseous canals, called the TSF, allow the axons to pass from the Rosenthal canal along the auditory nerve (modiolus) toward the CNS (Figs. 2 and 3).[50]

Throughout the control specimens, the length of the astrocytic processes toward the basal cochlear turn tended to be longer than those toward the middle and apical cochlear turns (Fig. 2 right). It was noted, however, that these astrocytic processes never entered into the TSF in any cochlear turn, even in the basal cochlear turn in controls. With the exception of those in the basal turn, the length of the astrocytic processes never exceeded approximately 75 μm.

Electrophysiological and Morphological Changes After Compression

In rats the CNS portion of the auditory nerve is relatively long, and hence, the TZ is situated within the IAC as in humans (Figs. 2 and 3).[15,53] Because of this anatomical relationship, the compression in the CPA cistern always injured the CNS portion where astrocytes are abundant.

Group A. One week after compression, the general shape of the ABR was preserved but the peak amplitudes were attenuated and the latencies of Waves II, III, and IV were prolonged (Fig. 4). The I–II IPL increased from 0.34 ± 0.03 msec before compression to 0.40 ± 0.03 msec (mean ± SD). The II–IV IPL increased from 0.64 ± 0.03 msec to 0.66 ± 0.04 msec (Fig. 5). The I–II IPL was significantly prolonged after compression ($p < 0.05$) but the II–IV IPL was not. After compression, an unlabeled region was observed just beneath the compression site (Fig. 6). Within this region, GFAP immunoreactivity was lost, indicating the mechanical disruption of the astrocytes. The shape of the TZ was essentially unchanged and the astrocytic outgrowth at the TZ was limited. In the cochlear nucleus we did not observe any change in GFAP staining (data not shown).

Eight weeks after compression the general configuration of the ABR was preserved but the peak amplitude was attenuated and the latencies of Waves II, III, and IV were prolonged (Fig. 7). The latency of the I–II IPL increased from 0.34 ± 0.02 msec to 0.41 ± 0.03 msec ($p < 0.05$) and the II–IV IPL decreased from 0.64 ± 0.01 msec to 0.63 ± 0.03 msec (not significant) (Fig. 5). There was no significant difference in the I–II IPLs between 1 week and 8 weeks after compression. Labeling for GFAP showed that the astrocytic processes elongated enormously from the TZ toward the PNS portion of the auditory nerve (Fig. 8A and B). The length of a substantial number of astrocytic processes was more than 200 μm. The elongated processes ran in parallel with the residual auditory neurons. They entered much further into the TSF in the basal portion of the cochlea compared with the middle cochlear turns (Fig. 8B and C). At the compression site, small, unlabeled areas were observed. Confocal images disclosed a dense meshwork of gliotic tissue at and in the vicinity of the lesion epicenter and fragments of neurons were scattered in this gliotic tissue (Fig. 8D). In the cochlear nucleus, hypertrophic astrocytic processes were abundant around the soma of the neurons (Fig. 8E *single asterisks*) in comparison with the control (Fig. 8F), and in a limited area they formed a meshlike structure of gliotic tissue (Fig. 8E *double asterisks*).

Group B. One week after compression, the ABR was hardly discernible (Fig. 9). Immunohistochemically, a large area unlabeled for GFAP was observed at the compression site (Fig. 10), and it was much larger than that observed in Group A (Fig. 6). The IAC was filled with swollen auditory nerve tissue, a finding not observed in any of the rats in Group A at either time point or in the Group B rats 8 weeks after compression (see below). Astrocytic outgrowth from the TZ was, however, limited (Fig. 10 *large arrowheads*) and in the cochlear nucleus there was no obvious change in GFAP staining (data not shown).

Eight weeks after compression, the peaks of the ABR could not be identified (Fig. 11). The growth of astrocytic processes was much more extensive than in Group A at 8 weeks postcompression (Fig. 12). The length of many processes was more than 300 μm. The astrocytic outgrowth was most evident at the basal portion of the cochlear turn, where the processes elongated and occupied all the orifices of the TSF. Confocal images showed that they ran parallel with the residual auditory neurons within the TSF. In the lesion epicenter, dense gliotic tissue surrounded neural tissue fragments. Similar dense gliotic tissue occupied the cochlear nucleus, where the neurons were tightly surrounded by ramified gliotic tissue. This pathology was only rarely observed in the Group A animals (Fig. 8E). The transverse diameter of the auditory nerve at and proximal to the compression site was reduced considerably, and this finding was more pronounced in this subgroup than in the Group A rats killed at 8 weeks (Figs. 12A and 8A, respectively).

Discussion

In this study we demonstrate for the first time that compression of the auditory nerve induces reactive gliosis not only in the auditory nerve but also in the cochlear nucleus. This can occur even with minimal degradation of the ABR. Thus, reactive gliosis should potentially be regarded as a "third causative factor," in addition to neural and vascular factors, for hearing loss following surgical treatment for VS.

Glial Scar Formation and Degree of Injury

Glial scars are formed in the adult CNS following various insults and constitute a physical and molecular barrier unfavorable to axon survival and regeneration.[6,41,49] In our present study, the gliotic tissue was observed at the lesion epicenter and in the vicinity of the compression site 8 weeks postcompression. Normal tissue architecture was lost, and fragments of auditory neurons were surrounded by reactive astrocytes (Figs. 8D and 12D). Reported ultrastructural findings of degenerating and degenerated

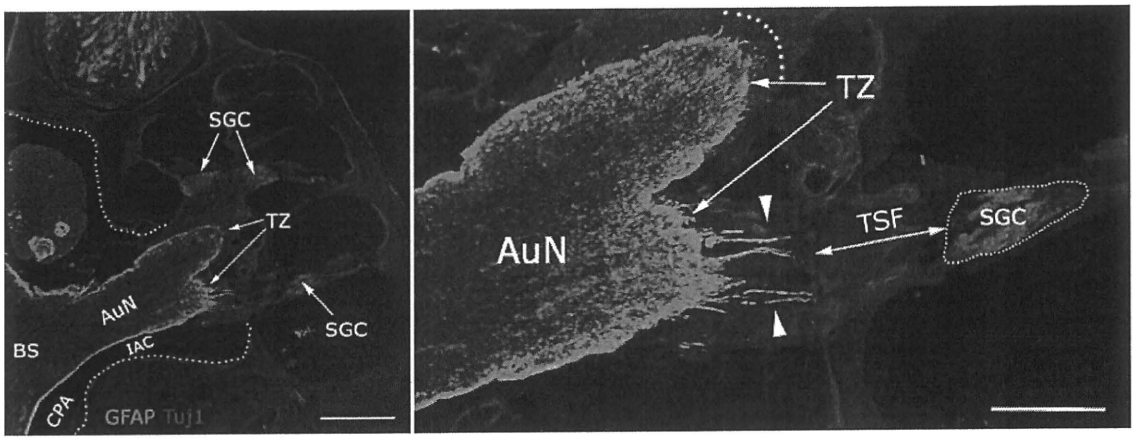

FIG. 2. Photomicrographs showing the TZ of the normal auditory nerve. The interface between the central and peripheral portions of the auditory nerve is clearly observed with anti-GFAP immunostaining *(green)* because of the presence of astrocytes only in the CNS portion of the auditory nerve. Note that the astrocytic processes toward the basal cochlear turn are longer than those toward the other cochlear turns (*arrowheads* in the **right panel**). The astrocytic processes never entered into the TSF in any cochlear turn even in the basal cochlear turn in controls. In this rat, the length of the astrocytic processes from the TZ was less than 75 μm, the longest distance of astrocytic extension in controls in all the cochlear turns except the basal turn (*dotted line* in the **right panel**). The *dotted line* in the **left panel** indicates the border between the intra- and extracranial compartments. Anti-GFAP and anti–beta III-tubulin (clone Tuj1) immunostaining. Bar = 500 μm (left) and 250 μm (right). AuN = auditory nerve; BS = brainstem; SGC = spiral ganglion cell.

axon terminals surrounded and phagocytosed by reactive astrocytes after deafferentation may correspond to our results.[4,10,17,23]

Our results also show that the higher level of compression applied to animals in Group B caused greater degradation of the ABR, increased astrocytic outgrowth from the TZ, higher levels of gliosis in the cochlear nucleus, and larger areas lacking GFAP labeling close to the compression site. In spinal cord injury, the hemorrhagic zone at the lesion epicenter cavitates as a result of necrosis several days after trauma.[22,55] Hemorrhagic foci have been observed previously within the auditory nerve trunk following mechanical trauma.[45] This study shows that they decrease between 1 and 8 weeks after surgery, suggesting invasion by reactive astrocytes. The observed swelling of the auditory nerve within the IAC was much less for low levels of compression and after the longer survival period. Hence, it is likely that swelling occurs only in acute stages of severely compressed auditory nerves, and that it is caused by edema as observed in the optic nerve.[25]

Astrocytic Proliferation and ABR Deterioration

In small experimental animals, Wave I of the ABR is generated from the extracranial (intratemporal bone) portion of the auditory nerve, Wave II reflects synaptic activity in the cochlear nucleus, and the subsequent waves reflect electrical activity in the pons/upper brainstem.[33,46] Because the compression site in our experiments was situated at the IAM, the IPL between Waves I and II was prolonged, but from Wave II through Wave IV the latencies were unaffected.

In our present study, the astrocytic processes elongated conspicuously from the TZ toward the PNS portion of the auditory nerve, ran parallel with the residual auditory neurons, and entered into the TSF, particularly

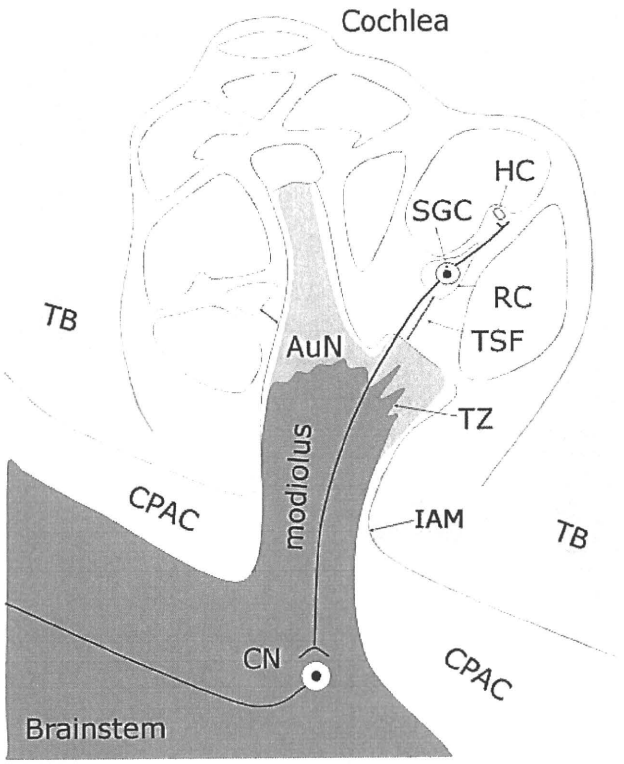

FIG. 3. Schematic illustration showing the anatomical relationships between the auditory nerve and the surrounding structures. The auditory nerve is a bundle of bipolar neurons that form synaptic contacts with the hair cells peripherally and cochlear nucleus cells centrally. The cell bodies of the auditory neurons (spiral ganglion cells) are housed in the Rosenthal canal. The TSF is an osseous canal through which the axons of the auditory nerve pass from the Rosenthal canal to the axis of the auditory nerve (modiolus). CN = cochlear nucleus; CPAC = CPA cistern; HC = hair cell; RC = Rosenthal canal; TB = temporal bone.

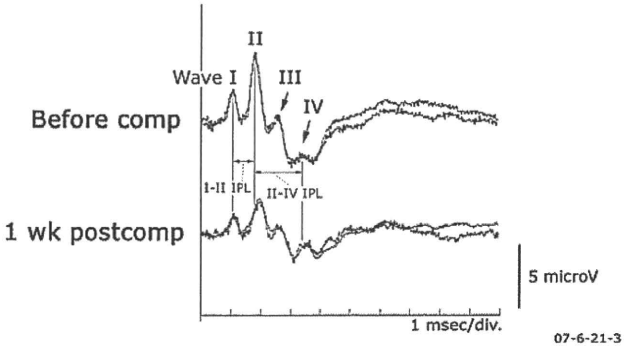

FIG. 4. Auditory brainstem responses in a Group A rat, before and 1 week after compression. The general configuration of the ABR was maintained after compression, but the amplitude of each peak was attenuated and the latencies of Waves II, III, and IV were prolonged. The IPL between Waves I and II (I–II IPL) and that between Waves II and IV (II–IV IPL) before compression are indicated by *doubleheaded horizontal arrows*. Comp = compression.

in the basal region of the cochlea. Massive proliferation of astrocytic processes within the modiolus may physically compress the adjacent nerve fibers, especially within the narrow canals of the TSF. If so, then this could be a cause of hearing loss. Moreover, enhanced glial activity in the region of the cochlear nucleus might have caused both structural and functional changes among synaptic complexes and postsynaptic neurons.[14,16,48] Progressive degeneration of axons has been reported to occur over 8 months and more than 1 year after peripheral insult to the auditory nerve/cochlear nucleus (noise-induced hair cell damage) and spinal cord injury, respectively.[35,57] Thus, the attenuation of Wave II of the ABR may have been caused both by reactive gliosis related to cochlear nucleopathy and by reduction of auditory nerve activity in the cochlear nucleus.

Within Group A, statistically significant differences in the I–II IPLs were not observed between 1 and 8 weeks after compression. However, some auditory nerve degeneration must have developed without being detected in the ABR recordings. Our fast Fourier transform analysis revealed that the click that we used included frequencies up to approximately 5 kHz. The stimulator used was designed for use in humans, and its power spectrum normally stimulates the apical, middle, and upper basal turns of the cochlea; in rats, however, it stimulates only approximately one-quarter of the length of the cochlea.[11,37,60] Thus, the ABRs in our experiments did not cover the potential electrophysiological changes associated with the auditory nerve dysfunction due to the massive outgrowth of astrocytic processes in the lower apical, middle, and basal turns. In one study on rats in which the cochlea was surgically removed, GFAP immunoreactivity increased in the cochlear nuclei 2 days after the surgery, remained intense for 3–8 days, and then declined by Day 21.[12] In another study, the GFAP reaction occurred on Day 1, increased in intensity at Days 4–21, and then remained elevated until Day 45 in the cochlear nucleus (the longest observation time in the study).[8] Our results suggest that

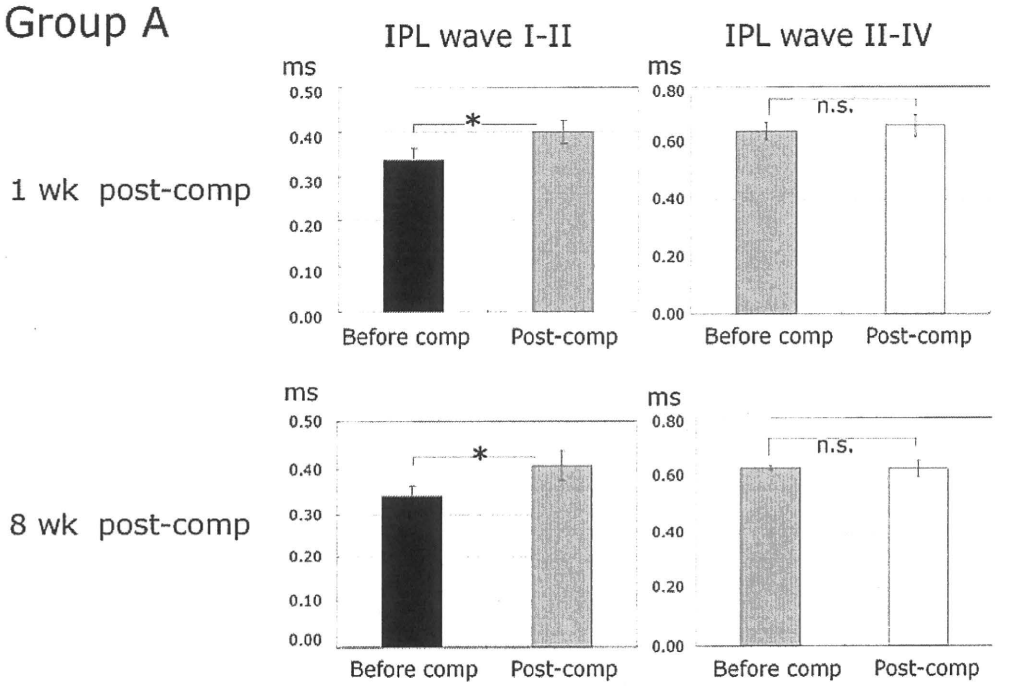

FIG. 5. Bar graphs showing the mean IPLs (± 1 SD) between Waves I and II (I–II IPL) and between Waves II and IV (II–IV IPL), 1 week and 8 weeks after compression in Group A. The I–II IPL was significantly prolonged after compression but the II–IV IPL was not. There was no significant difference between the I–II IPL at 1 week and that at 8 weeks postcompression. ms = msec; n.s. = not significant. * $p < 0.05$.

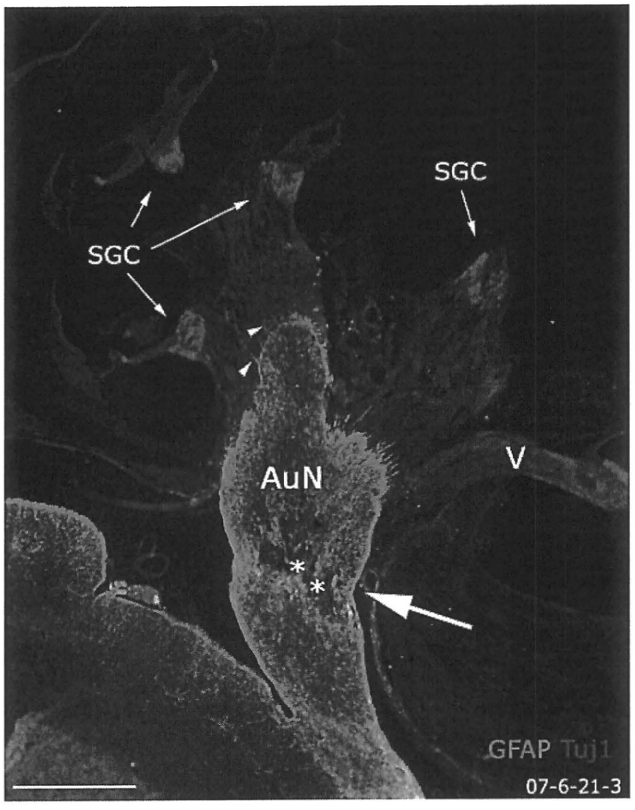

FIG. 6. Photomicrograph showing morphological changes in the auditory nervous system 1 week after compression in Group A (the same rat as in Fig. 4). A GFAP-negative region *(asterisks)* was observed at the compression site *(arrow)*. The shape of the TZ was essentially unchanged *(arrowheads)*. Anti-GFAP and anti–beta III-tubulin (clone Tuj1) immunostaining. Bar = 500 μm. V = vestibular nerve.

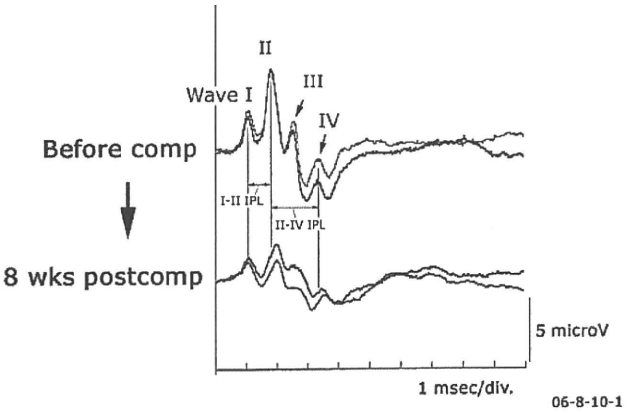

FIG. 7. Auditory brainstem response in a Group A rat, before and 8 weeks after compression. The amplitude was attenuated, but each peak of the ABR was preserved while the latencies of Waves II, III, and IV were prolonged. The I–II IPL and II–IV IPL before compression are indicated by *doubleheaded arrows*.

reactive gliosis continues at least to the 8th week post-compression, and longer-term studies are needed to describe the full consequences of the response.

Clinical Extrapolations

Various clinical observations can be explained by reactive gliosis combined with the previously reported pathophysiological mechanisms. Several reports have demonstrated that the presence of adhesion in the interface between the auditory nerve and the tumor is the most significant negative prognostic factor in hearing preservation surgery, regardless of tumor size.[24,36,51,61] The less adhesion, the less mechanical force needed to separate the auditory nerve from the tumor surface, leading not only to less trauma-induced auditory nerve degeneration but also to less reactive gliosis.

"Cochlear nucleopathy" may "naturally" occur as a VS increases in volume. As the cochlear nuclei are located at the entrance of the fourth ventricle[1] and the shape of the fourth ventricle is inevitably distorted in accordance with tumor growth, the cochlear nuclei cannot escape from the effects of mechanical stress and reactive gliosis. In patients with neurofibromatosis Type 2, the outcome of auditory brainstem implant placement was less favorable in those cases in which the VS compressed and distorted the brainstem than in those in which it did not.[31] In the former, reactive astrocytic proliferation in the cochlear nuclei may have modified synaptic organization leading to less effectiveness of the implant, although larger tumors can be expected to cause more advanced degeneration than smaller ones.

There are some caveats with respect to extrapolation from our results to the situation in human patients. First, the length of the auditory nerve differs markedly between rats and humans. In rats the cisternal portion is approximately 0.5 mm at most (Fig. 2), whereas in humans it is approximately 10–15 mm.[26,34,54] Reactive gliosis may be more severe where the compression site is so much closer to the brainstem.[29,42] Second, in our study the changes to the ABR were created on purpose by traumatizing the "normal" auditory nerve. Under clinical conditions, trauma to the normal auditory nerve may be very rare. In the clinical setting, the ABR configuration in patients with VS is often already distorted before surgical intervention, with the tumor mass causing auditory nerve dysfunction through mechanical compression. This is especially the case with respect to the intracanalicular portion of the auditory nerve. In a study in which the intracanalicular pressure was directly measured in the patients with VS, the pressure within the IAC was significantly elevated, and the authors concluded that pressure from tumor growth in the IAC might be responsible for hearing loss.[3] The morbid auditory nerve in the patients with VS could be significantly more sensitive to the same insult than the normal auditory nerve.[27] Third, we observed ABR decline and remarkable astrocytic proliferation 8 weeks after compression. In contrast, delayed hearing loss has been reported years after surgery in patients who have undergone VS surgery with preserved hearing.[5,9,18,32,58,59] Therefore, our results may be better applied to "subacute" hearing loss in VS surgery. Typically, these patients wake up with hearing after surgery but suffer hearing loss 1–2 months later. However, the time course in gliosis may be different in humans and rats, and it is important to carry

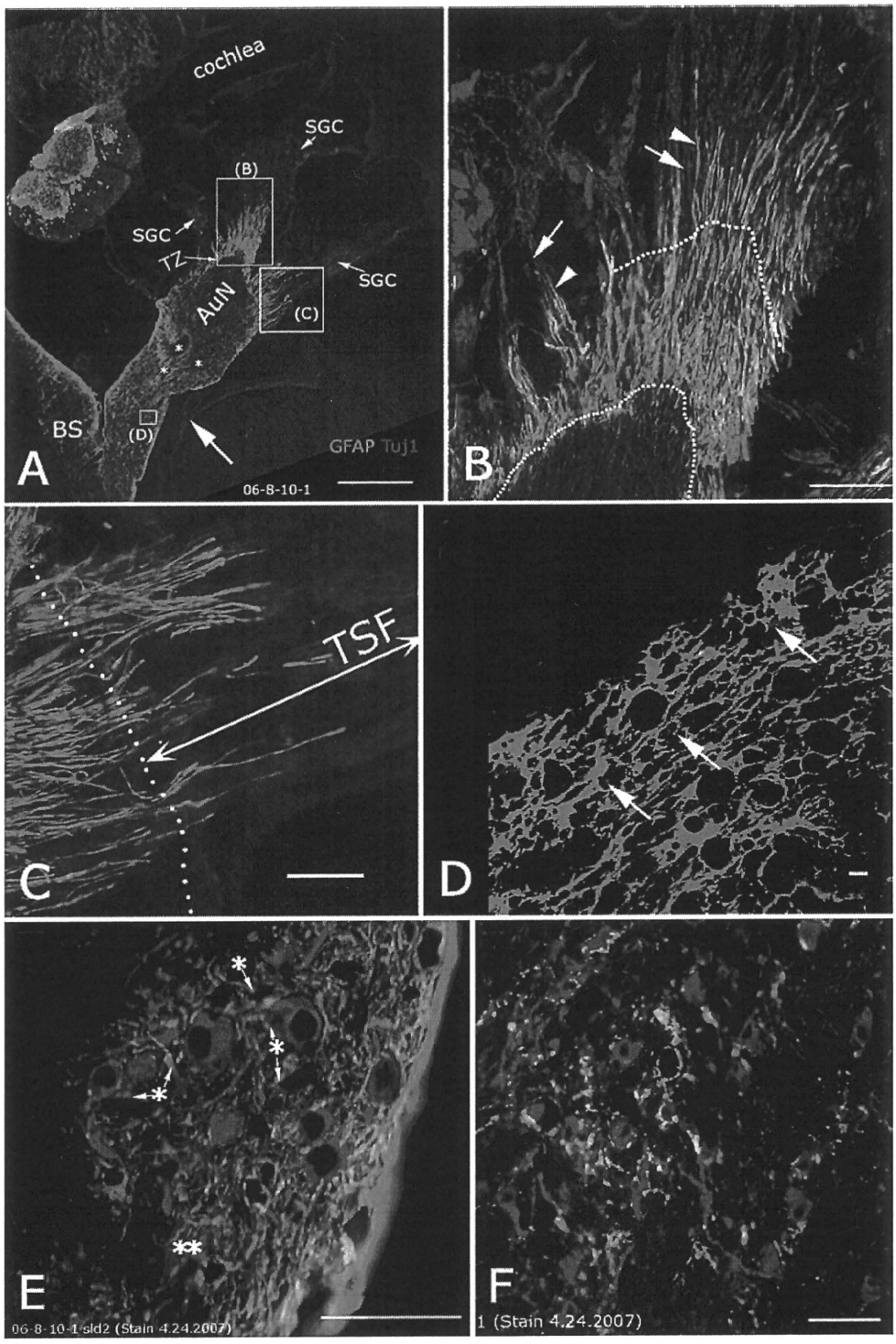

Fig. 8. Morphological changes in the auditory nervous system 8 weeks after compression in Group A (the same rat as in Fig. 7). The astrocytic processes elongated enormously from the TZ toward the periphery (**A and B**). The length of many astrocytic processes was more than 200 μm from the TZ (*dotted lines* in **B**) and they ran parallel with the residual auditory neurons (the *arrowhead* in **B** indicates an astrocytic process and the *arrows*, auditory neurons). The astrocytic processes penetrated the TSF more deeply in the basal portion of the cochlea **(C)** than in the middle portion **(B)**. (Panels **B and C** are enlargements of areas indicated by "(B)" and "(C)" in **panel A**.) At the compression site (*large arrow* in **A**), small, unlabeled areas were observed (*asterisks* in **A**). At and in the vicinity of the lesion epicenter, a dense meshwork of gliotic tissue containing the fragments of neurons (*arrows* in **D**) was observed (the area indicated by "(D)" in **panel A** is enlarged in **panel D**). Hypertrophic astrocytic processes were observed in the cochlear nucleus (*single asterisks* in **E**). Meshlike structure of gliotic tissue was occasionally seen (*double asterisks* in **E**). **F:** Cochlear nucleus region in control. Anti-GFAP and anti–beta III-tubulin (clone Tuj1) immunostaining. Bar = 500 μm (A), 100 μm (B), 100 μm (C), 10 μm (D), 50 μm (E), and 50 μm (F).

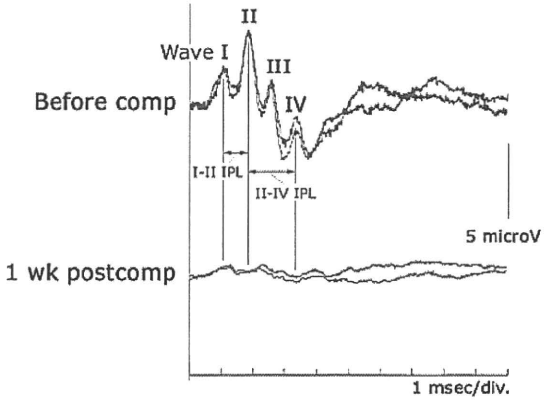

FIG. 9. Auditory brainstem responses in a Group B rat before and 1 week after compression. All the components of ABR were hardly discernible after compression. The I–II IPL and II–IV IPL before compression are indicated by *doubleheaded arrows*.

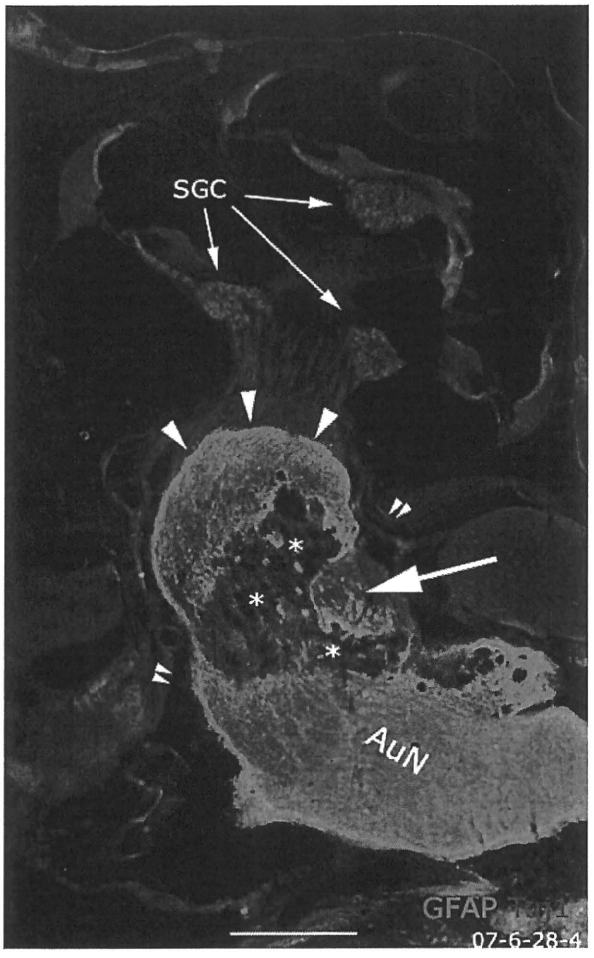

FIG. 10. Morphological changes in the auditory nerve 1 week after compression in a Group B rat (the same animal as in Fig. 9). A large area unlabeled for GFAP *(asterisks)* was observed at the compression site *(arrow)* (compare with Fig. 6). The IAC was filled with swollen auditory nerve tissue. Astrocytic outgrowth from the TZ was limited *(large arrowheads)*. *Small double arrowheads* indicate the IAM. Anti-GFAP and anti–beta III-tubulin (clone Tuj1) immunostaining. Bar = 500 μm. Original magnification × 2.

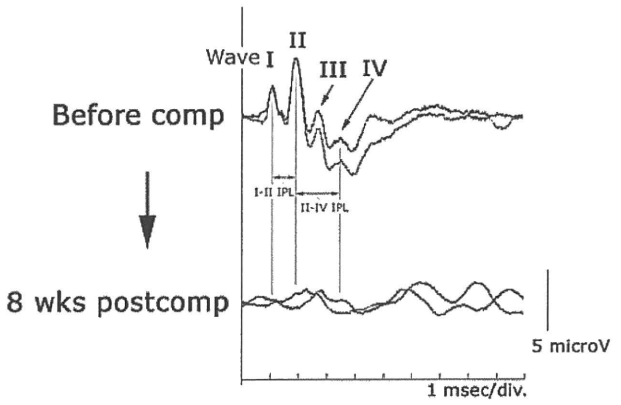

FIG. 11. Auditory brainstem responses in a Group B rat before and 8 weeks after compression. The waveform was not visible after compression. The I–II IPL and II–IV IPL before compression are indicated by *doubleheaded arrows*.

out short- and long-term studies of sequential ABR tracings following surgery in human patients.

Conclusions

We applied compression, a constituent mechanical factor in complex operative procedures, to the auditory nerve of rats while recording ABRs to measure the related hearing loss quantitatively. We found for the first time that a substantial reactive gliosis occurs in both the peripheral and central auditory pathways within 1–8 weeks and is associated with significant degradation of the ABR. This finding warrants further research to test the possibility that in the longer term the gliosis may correlate with and may even cause continued hearing loss. Reactive gliosis may be a primary cause of progressive hearing loss following microsurgical treatment for VS.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. This study was supported by the Ministry of Education, Culture, Sports, Science and Technology (Japan), the General Insurance Association of Japan, and the Univers Foundation (Japan).

Author contributions to the study and manuscript preparation include the following. Conception and design: T Sekiya. Acquisition of data: T Sekiya, M Matsumoto, K Ono, S Kada, H Ogita, RT Horie, A Viola. Analysis and interpretation of data: T Sekiya, K Ono, MC Holley. Drafting the article: T Sekiya. Critically revising the article: T Sekiya, MC Holley. Reviewed final version of the manuscript and approved it for submission: T Sekiya, M Matsumoto, K Kojima, K Ono, YS Kikkawa, S Kada, H Ogita, RT Horie, A Viola, MC Holley, J Ito. Statistical analysis: T Sekiya. Study supervision: J Ito.

Acknowledgments

The authors appreciate Dr. Agneta Viberg for her useful discussion, and Keiko Nishio, Koichiro Shimomura, Kazumi Sugimoto, and Masashi Higashino for their technical assistance and animal care.

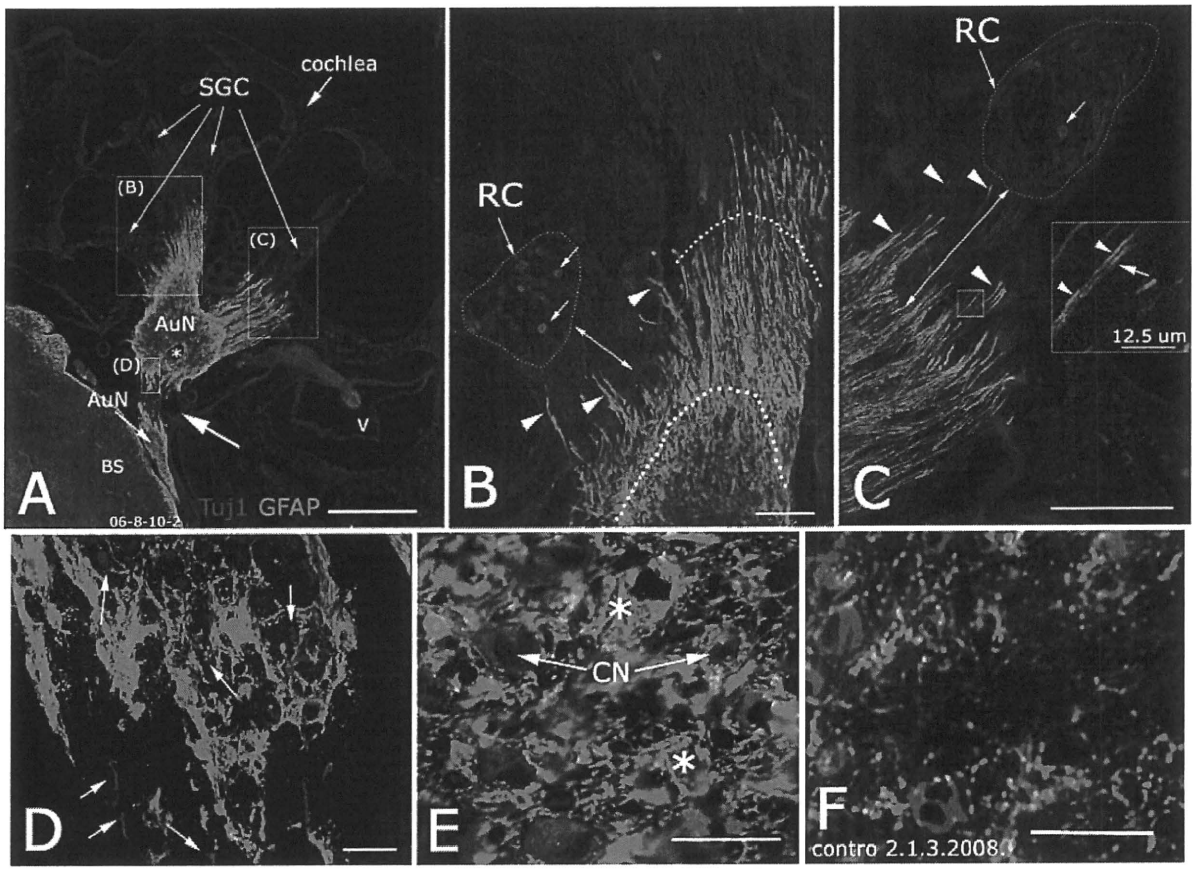

FIG. 12. Morphological changes in the auditory nervous system 8 weeks after compression in a Group B rat (the same animal as in Fig. 11). Extensive astrocytic outgrowth from the TZ was evident (**A–C**). The length of many astrocytic processes was more than 300 μm from the TZ (*dotted lines* in **B**). In the basal turn of the cochlea where the astrocytic outgrowth was greatest, the elongated processes occupied all the orifices of the TSF (*arrowheads* in **C**). The rectangle in C is enlarged in the **inset**; the astrocytic processes (indicated by *arrowheads*) ran parallel with the residual auditory neurons (indicated by *arrow*). In the lesion epicenter, dense plexiform gliotic tissue surrounded neural tissue fragments (*arrows* in **D**). Multiple, small areas unlabeled for GFAP were observed at the compressed site (*asterisk* in A). In the cochlear nucleus, neurons were surrounded by dense gliotic tissue (*asterisks* in **E**; cochlear nucleus region in control, **F**). The transverse diameter of the auditory nerve at and proximal to the compression site was reduced in comparison with that in the Group A rats at 8 weeks postcompression (Fig. 8). The *small arrows* in the Rosenthal canals in **B and C** indicate the residual spiral ganglion cells after compression. Anti-GFAP and anti–beta III-tubulin (clone Tuj1) immunostaining. Bar = 500 μm (A), 100 μm (B), 200 μm (C), 25 μm (D), 25 μm (E), and 25 μm (F).

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Manuscript submitted December 6, 2009.
Accepted February 16, 2010.
Please include this information when citing this paper: published online April 2, 2010; DOI: 10.3171/2010.2.JNS091817.
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シリーズ　知っておきたい生理・病態の基礎

8. 聴覚末梢

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第82巻　第9号 別刷
2010年8月20日 発行

医学書院

耳喉頭頸　82(9)：631-635，2010

シリーズ　知っておきたい生理・病態の基礎

8．聴覚末梢

狩野 章太郎*

Ⅰ はじめに

蝸牛において有毛細胞の上部では基底板の振動が受容器電位に変換され（mechanoelectrical transduction），内有毛細胞と聴神経をつなぐシナプスでは受容器電位がスパイク列に変換される。Mechanoelectrical transduction は外有毛細胞の増幅機構にも関与している。有毛細胞の上下という狭い領域にこのような精緻な機構が存在し，今までは不明な点が多かったがこの 10 年で画期的な知見が続々と得られている。

Ⅱ 内・外有毛細胞の形態と聴神経の接続

ヒトでは一側の耳で 3 万本の聴神経線維が存在する。求心性線維は蝸牛の有毛細胞と脳幹の蝸牛神経核を接続する。らせん神経節細胞の 5〜10% が外有毛細胞に接続し，残りが内有毛細胞に接続する[1]。約 20 本の求心性線維が 1 個の内有毛細胞に，また約 6 本の求心性線維が 1 個の外有毛細胞に接続する。内有毛細胞では不動毛は緩い弧状に並び，外有毛細胞では W 字状に並ぶ（**図 1**）。

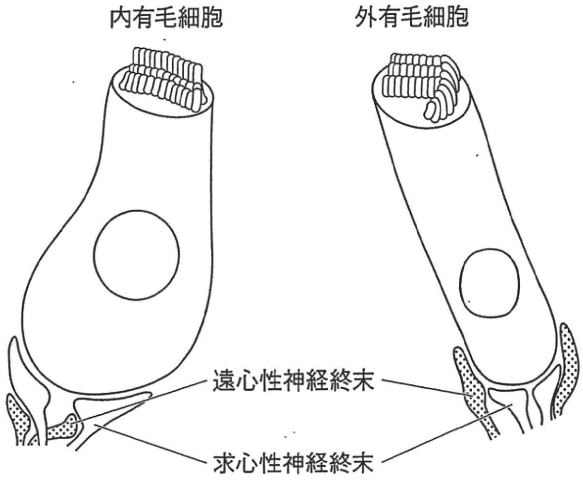

図 1　有毛細胞と聴神経との接続

Ⅲ 有毛細胞の mechanoelectrical ransduction

有毛細胞は不動毛のわずかな屈曲にも敏感に反応し，聴力閾値付近では不動毛の動きは 1 nm 以下と推定される[2]。不動毛はアクチン線維で構成され，不動毛同士は lateral link および ankle link によって連結され束として動く。短いほうの不動毛の先端と長いほうの不動毛をつなぐ tip link があり，不動毛の動きを mechanoelectrical transducer（MET）チャンネルに結びつける[3]（**図 2**）。Tip link を破壊すると mechanoelectrical transduction は障害され，tip link が再生すると回復した[4]。不動毛の束が長い不動毛の方向に傾くと，MET チャネルが開いてカルシウムイオンが細胞内に流入して脱分極が起こる。短い不動毛方向に傾くと MET チャンネルが完全に閉じて相対的に過分極になる。最近の研究で MET チャンネルは tip link の下端側にだけ存在することが明らかになった[5]。

MET チャンネルが tip link に直接結合してい

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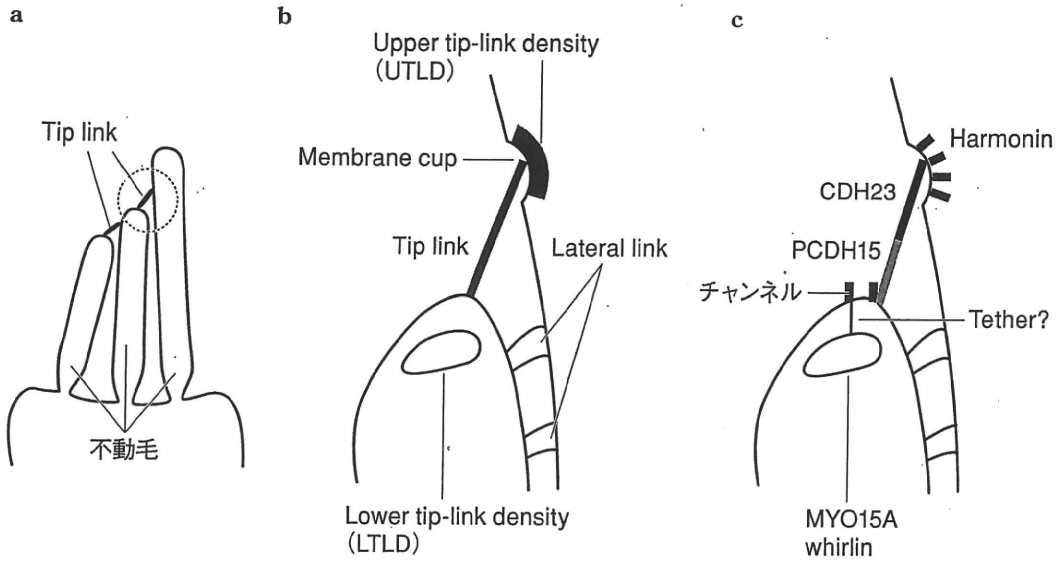

図 2　Hair bundle の構造

a：不動毛と tip link 円内の拡大を b に示す，b：tip link 周辺の構造を示す。
c：b の構造に対応する分子を示す。短いほうの不動毛に mechanoelectrical transducer チャンネルが存在する。

〔文献 6 を一部改変して引用〕

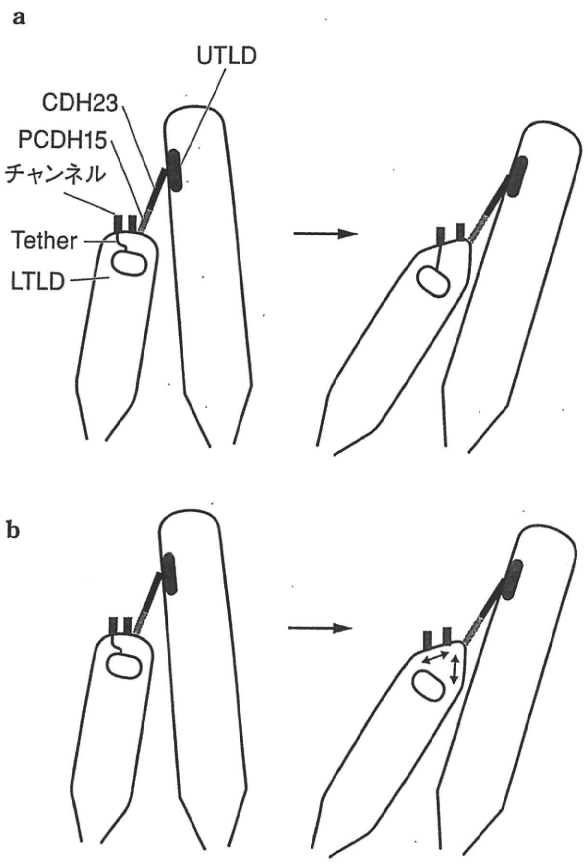

図 3　MET チャンネルが開く機構のモデル

a：MET チャンネルが tip link に直接結合していて不動毛が傾くとチャンネルが開くというモデル
b：細胞膜の張力増加によりチャンネルが開くというモデル

〔文献 6 から一部改変して引用〕

て不動毛が傾くとチャンネルが開くという説と，膜の張力が増大してチャンネルが開くという説がある[6]（図 3）。MET チャンネルは 10 マイクロ秒以内という速度で開くことができ mechnoelectrical transduction のスピードを説明できるが，酵素の働きや拡散ではこのスピードを説明できない[7]。1 本の不動毛当たりの MET チャンネルは 1〜2 個と推定されている[8]。Tip link を構成する分子〔カドヘリン 23（CDH23）やプロトカドヘリン 15（PCDH15）〕が明らかになったのは近年であり[9,10]，MET チャンネルの候補としては transient receptor potential（TRP）チャンネルが挙げられているが，チャンネルの物理的特性が完全には一致せず結論は出ていない[11]。

Ⅳ 有毛細胞の mechanoelectrical transduction とプレスチン

有毛細胞の毛の動きはたかだか 100 nm 程度に過ぎないにもかかわらず，検知できる音圧の範囲（ダイナミックレンジ）は大きい。そのため内有毛細胞が音の情報を聴神経に伝える前の段階で，小さな音圧の刺激は大きな音圧の刺激よりもより強く増幅される必要がある（非線形性）。基底板は音の振動数にあわせて振動するが，その上にのっている外有毛細胞が能動的に動くことで，基底板の

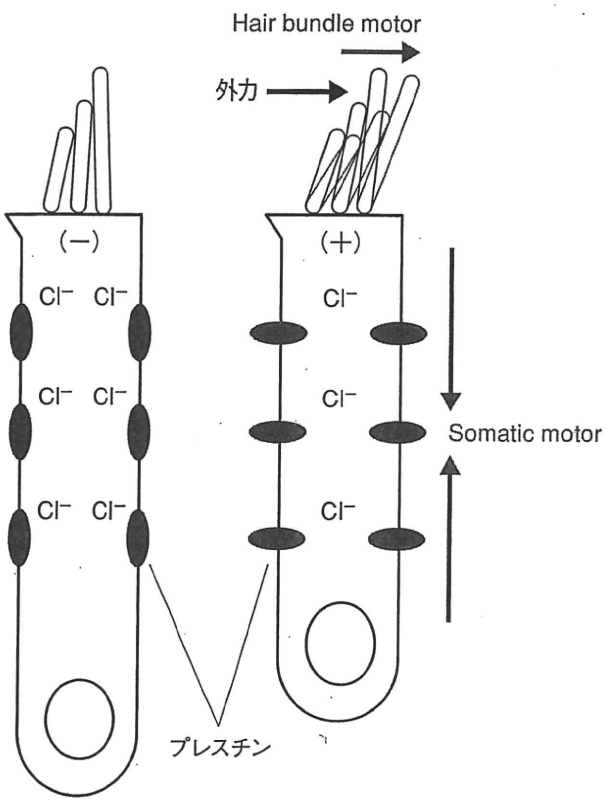

図 4　外有毛細胞が基底板の振動を増幅する機構
静止膜電位（−）においては塩素イオンは膜上の分子プレスチンに結合しているが，不動毛が倒れて脱分極（+）が起こると塩素イオンが外れてプレスチンの立体構造が変わり，外有毛細胞が長軸方向に縮む（somatic motor）。また外力により不動毛が倒れると，不動毛に外力と同じ方向の力が生じて positive feedback が起こる（hair bundle motor）。
〔文献 13 から一部改変して引用〕

振動が増強される。この過程には 2 つの機構が想定されている（**図 4**）。

1 つは外有毛細胞の外側壁に存在する膜蛋白，プレスチンによるもので，somatic motor と呼ばれる。哺乳類の外有毛細胞は電気刺激によって伸縮することが知られている。前項で述べたように，不動毛が倒れて MET チャンネルが開くと外有毛細胞は脱分極する。静止膜電位のときには塩素イオンがプレスチンに結合しているが，脱分極が起きると塩素イオンが外れてプレスチンの立体構造が変化し，細胞膜上に占める面積が小さくなるために外有毛細胞が縮む[12,13]。

もう 1 つは hair bundle motor と呼ばれる。不動毛が倒れて MET チャンネルが開くとカルシウムイオンが細胞内に流入する。このときラットの場合は不動毛に外力と同じ方向の力が生じて positive feedback が起こることが明らかになっている[14]。MET チャンネルから流入するカルシウムイオンが，脱分極を経てプレスチンによる somatic motor を活性化するほど大きくなくても，hair bundle motor は機能する。Somatic motor は脱分極が必要なので膜の時定数に制限されて高周波の振動に対応できないが，hair bundle motor は高速の MET チャンネルの開閉スピードにのみ制限されるので高周波音の増幅にも対応できると考えられている。

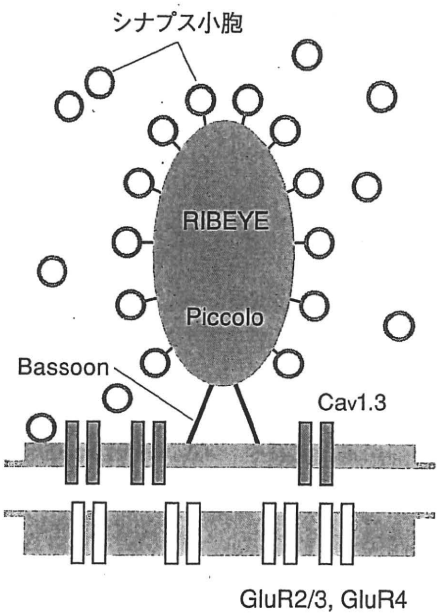

図 5　有毛細胞の active zone に存在するリボンシナプスを構成する分子
〔文献 16 を一部改変して引用〕

Ⅴ 内有毛細胞と聴神経のシナプス

哺乳類では求心性線維の分岐しない樹状突起の 5〜30 本が 1 つの内有毛細胞とシナプスを形成している[15]。既に all or none の活動電位から始まる通常のシナプスと異なり，リボンシナプスは，アナログ情報である受容器電位を活動電位に変換しなければならない。この過程は，音刺激の特定の位相に同期した聴神経の発火（phase locking）を実現するため，高い時間的精度が求められる。このシナプスは，神経伝達物質を高い時間的精度で連続的に放出するため特化したリボンシナプスと呼ばれ，特別な仕組みがある（**図 5**）[16]。

有毛細胞の受容器電位の変化により，L 型電位依存性カルシウムチャンネル（$Ca_V1.3$）が開いて細胞内カルシウム濃度が増加し，神経伝達物質が

シナプスに放出される。このカルシウムチャンネルはシナプス小胞の多い active zone と呼ばれる狭い領域に集中して存在し，局所的なカルシウム濃度が高くする。1つの active zone に1つのシナプス後端末が接している。さらに1つの active zone に細胞膜につながれたリボンと呼ばれる構造が存在し，その周囲に輪状につながれたシナプス小胞が存在する[17]。リボンの主体は RIBEYE と呼ばれる蛋白質である[18]。Bassoon や Piccolo と呼ばれる分子がリボンを active zone に繋いでいる。Bassoon の遺伝子欠損マウスで放出用のシナプス小胞が減少して，シナプス伝達が不十分になっており[17]，auditory neuropathy との関連が示唆される。

音の周波数をコードするために，このカルシウムチャンネルは 300 マイクロ秒程度の速い時定数をもち，成体では不活化が起きにくくなっており，神経伝達物質を持続的に放出できるので，連続的なシナプス伝達に適している[19,20]。カルシウム濃度の急速な変化に対応するためカルシウム結合蛋白などによる緩衝機能も速い時定数をもつと推定されている[21]。欠損すると難聴の原因となる遺伝子 Otoferlin は，内有毛細胞でカルシウムを検知してシナプス小胞のエキソサイトーシスを引き起こすと考えられているがまだ議論が分かれている[22,23]。有毛細胞内の急激なカルシウムイオン濃度上昇に反応して，マウスの内有毛細胞では最高で1秒間に 3×10^7 個程度のシナプス小胞のエキソサイトーシスが起こる[24]。リボンの存在によりシナプス小胞が active zone に集中していることがシナプス伝達の潜時を短くしている[25]。エキソサイトーシスに続いて細胞内に形成されていたシナプス小胞が即座に補充される[26]。受容器電位の生理的な範囲（−50〜−30 mV）では，カルシウムイオンの細胞内流入と求心性線維の活動の関係は線形であり，音圧のコードに歪みが少ないことを意味する[27]。内有毛細胞でグルタミン酸をシナプス小胞に充塡するのは vesicular glutamate transporter3（VGLUT3）であり，この遺伝子が欠損したマウスでは，後述のシナプス後端末の AMPA 受容体が機能していてもシナプス後電流が生じなかった[28]。

シナプス間隙に放出された神経伝達物質は聴神経側のシナプス後端末に存在する AMPA 型グルタミン酸受容体を刺激する[29]。マウスに音響外傷を与えると AMPA 受容体が減少し，その後聴力閾値が改善するとまた増えることが示されており，AMPA 受容体によりシナプス伝達の効率を最適化している可能性が示唆される[30]。聴神経には NMDA 受容体も存在し，サリチル酸が存在すればこれがアラキドン酸の濃度を上げ，NMDA 受容体が刺激されて聴神経の発火頻度を高める[31]。これは NMDA 受容体により聴神経の活動が調整されていることを示唆し，サリチル酸による耳鳴りのモデル[32]に合致する。

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Clinical Neuroscience Vol.29 No.4 2011年4月1日発行(毎月1回1日発行) 1984年1月23日第3種郵便物認可

Clinical Neuroscience

月刊 臨床神経科学

最新の治療デバイス

2011 Vol.29 4

中外医学社

人工内耳

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はじめに

平成18年度厚生労働省の報告で本邦における聴覚障害者の人数は27万人にのぼるといわれ，先天性高度難聴児の出生割合も1000人に1人と報告されており，高度難聴者の人数は決して少ない数字ではない[1]．補聴器は難聴の種類・程度によっては非常に有効な手段となるが，高度感音難聴者に対してはコミュニケーションに必要十分な聴覚補償が得られにくいというのが現実である．補聴器の装用効果がない高度難聴患者への新たな聴覚補助手段として，人工内耳は1970年代後半に開発，1980年代より臨床応用が始まった[2]．本邦でも1985年より導入，1994年には保険適用の認可がおり全国的に普及しつつある．人工内耳装用により，これまで補聴器では語音聴取がほとんど不可能となった中途失聴者が，人によっては携帯電話で会話ができるまで聴取能の回復を認めるようになった．また，先天性高度難聴児が人工内耳装用で療育次第では普通小学校へ通うことができるだけの口話コミュニケーション能力を獲得することも可能となった．本稿では人工内耳の原理，手術適応，問題点，将来展望について紹介する．

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聴覚と人工内耳

外界に存在する音は外耳道から進入し，鼓膜を振動させる．鼓膜の内側すなわち中耳に存在する耳小骨は鼓膜の振動を受けて，前庭窓より内耳へと振動を伝える．振動を受けた内耳は蝸牛内の基底板の振動をもたらし，蝸牛有毛細胞の聴毛と外膜にずれ運動が生じる．これにより有毛細胞の電気的発火がおこり，有毛細胞へ接続する神経線維，さらに，らせん神経節へと興奮が伝わり，電気的に音情報が中枢へと伝えられる(図1)．高度難聴の多くの原因は内耳の障害とされ，音振動が電気的刺激に変換できないことに起因する．人工内耳の原理は，内耳へ電極を挿入し，音信号に対応した電気的刺激を有毛細胞の代わりに直接神経へ伝えようというものである．蝸牛は2.5回転ある渦巻状の形状をなすが，基底部(基底回転)は高周波数の音感知を担い，頂上部(頂回転)は低周波数の音感知を行っている．人工内耳の蝸牛内に挿入される電極数は12～22個とメーカーにより異なるが，いずれの機種も基本的に外界の音の周波数分析を行い，それぞれに対応した神経線維，らせん神経節を刺激することでその情報を伝達し，音の強さは電流量により調節している．周波数の分析方法や電極の刺激

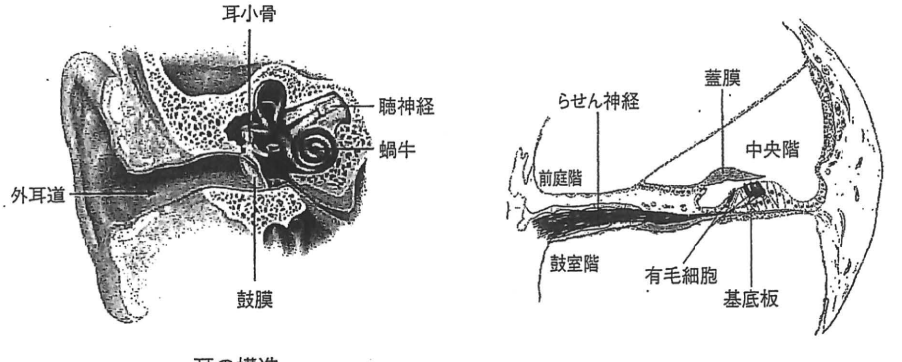

図1　耳の解剖〔左）Medel社資料より改変，右）野村ら[10]より改変〕

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発生方法などはコード化法といい，各社で研究が進められて日々進歩している状況である．

人工内耳の適応

各国により若干異なった基準があるが，ここでは本邦における人工内耳の適応基準を紹介する．本邦では成人の場合(18歳以上)と小児の場合に分けて基準が作成されている．成人の場合は比較的単純で，要約すると，

① 原則両側90 dB以上の高度難聴者で，かつ補聴器の装用効果がないもの

② 画像的所見で人工内耳挿入が可能であるもの

③ その他重篤な合併症がないもの

とされている．すなわち，人工内耳は補聴器の効果がない人が対象となり，補聴器装用で会話が可能な患者は人工内耳の適応とはなり得ない．一般的には補聴器装用下で単音節聴取能50%以下が適応といえる．重篤な合併症とは活動性中耳炎，重度の精神障害，聴覚中枢の障害などである．小児の場合は少々複雑で，抜粋すると，

① 術前から術後の療育に至るまで，家族および医療施設内外の専門職種との一貫した協力体制がとれている．

② 原則1歳6ヵ月以上

③ 原則両側90 dB以上の高度難聴者で，6ヵ月以上の補聴器装用で言語獲得に必要な補聴効果が得られないと予想されるもの

④ 活動性中耳炎がないこと

とされている．成人例と異なりその多くは言語獲得期以前からの難聴があるため，人工内耳の目的は言語獲得となる．言語獲得を成し遂げるためには，人工内耳挿入後のハビリテーションが重要な役割を果たす．このためには乳幼児の聴覚障害に熟知している医療者，難聴者に対する言語聴覚コミュニケーション指導の可能な療育機関，そして言語獲得に向けての家族の一致団結した取り組みが適応の大前提となってくる．このうえで初めて医学的な適応条件が含まれてくることになる．海外の報告でも早期年齢の手術が言語獲得に有利に働くとの結果が報告されている[3]とおり，早期の手術の重要性が認識されつつあり，本邦でも適応年齢が2006年に2歳から1歳6ヵ月に引き下げられた経緯がある．ただし，乳幼児の聴力を判断することは決して容易ではなく，高度難聴の診断には慎重を要するのも事実である．この意味でも専門的な医療機関での聴力評価，6ヵ月以上にわたる補聴器装用・療育などによる言語発達の経過観察期間が極めて重要な意味を持ってくる．活動性中耳炎，または反復性中耳炎は術後人工内耳感染・髄膜炎などのリクスがあるため，適応は慎重に行う必要がある．画像所見で人工内耳挿入のスペースの確認できない場合や高度内耳奇形症例は，禁忌ではないが慎重な判断が求められる．内耳奇形があっても，蝸牛不全分離や前庭水管拡大症などの軽度の奇形の場合，成績は比較的良好である．一方，内耳道狭窄や蝸牛低形成など高度の奇形を伴うものではその成績は不良である[4]．また，重複障害・中枢性聴覚障害も禁忌とはされていないが，言語獲得の面ではその効果は限定的にならざるを得ない．このような症例では，人工内耳の効果の限界につき，家族にもそのエンドポイントを理解してもらったうえで手術適応を決定することが必要である．

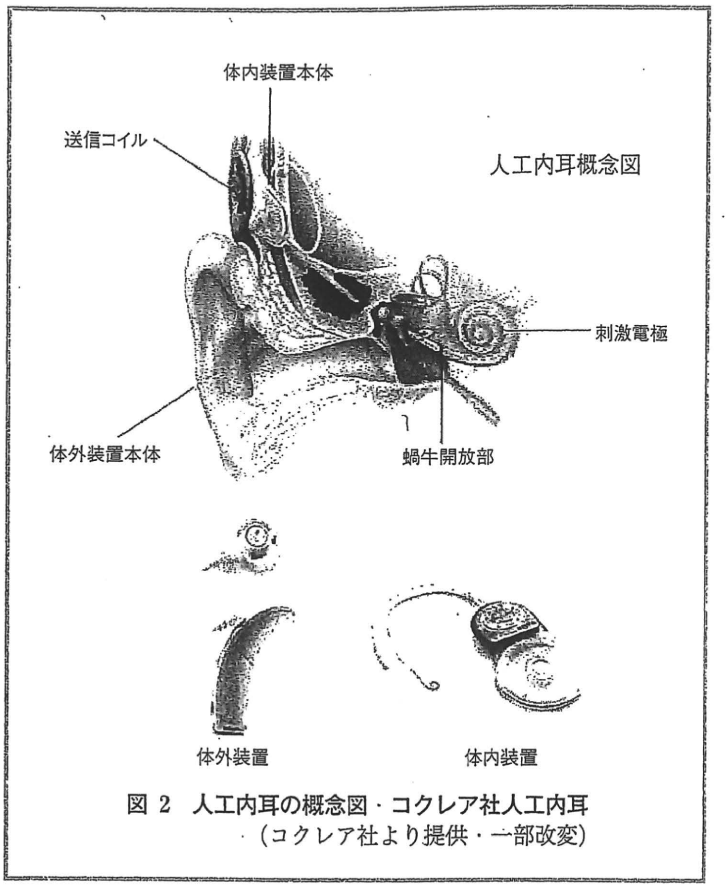

図2 人工内耳の概念図・コクレア社人工内耳
(コクレア社より提供・一部改変)

人工内耳手術の実際

人工内耳は外界の音を収集し周波数分析を行い電気的信号に変換する体外装置，および体外装置より得た信号を電

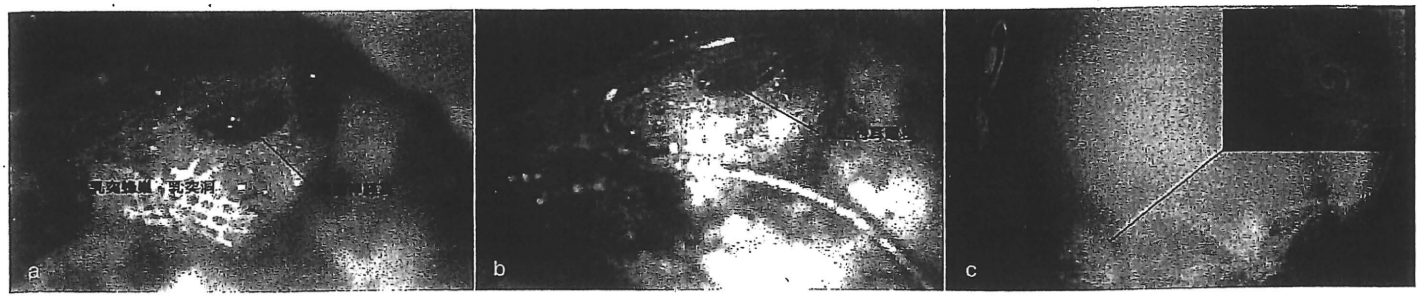

図 3　人工内耳手術

a）顔面神経窩を開放後，蝸牛を開放した．b）コクレア社 Nucleus Freedom CA 人工内耳挿入．
c）術後頭部単純 X 線にて蝸牛内に人工内耳が挿入されていることを確認した．

極を通じて蝸牛内で発信する体内装置に分けられる(図2)．体外装置は補聴器と同様に耳介に装着し，後頭部の体外部送信コイルより，分析・変換した電気的信号を体内装置へ電磁波として伝達する．電磁波を受け蝸牛内へ電気的刺激を伝達する役割を果たす体内装置は手術的に頭部および蝸牛内へ埋め込む必要がある．体内装置の本体は通常耳介後上方の皮下に固定する．電極は側頭骨の乳突部削開を行い，顔面神経窩を開放して鼓室内へ通路を設け，蝸牛の鼓室階に挿入するのが一般的である(図3a，b)．人工内耳手術では蝸牛を開放し，電極を挿入するという侵襲的な操作を加えるため，基本的に残存聴力は消失しやすい．また，その影響が前庭に及び，術後眩暈をきたすこともある．鼓室への到達経路である顔面神経窩を開放する際は顔面神経および鼓索神経の約2 mm 程度の間隙部分を削開する必要があり，両神経の損傷リスクが生じる．ただし，顔面神経については術中にモニタリングを行い確認するため頻度は極めて少ない．創部感染は術直後にも期間をあけても生じることもあり，常に気をつけなければならない．感染が悪化し人工内耳に感染が及ぶと，最悪の場合は本体の露出につながり摘出が必要となるため，早期の対応が重要となる．高度内耳奇形の場合，内リンパの脳脊髄液との交通が広い場合があり，その場合蝸牛開放の際に脳脊髄液の噴出(cerebro-spinal fluid gusher)を生じることがある．また，内耳奇形，および耳硬化症などによる蝸牛の脱灰が強い場合，誤挿入をきたすことが稀に存在する．術後X線・CTなどで挿入位置を確認することが重要である(図3c)．内耳奇形や蝸牛脱灰症例では加えて，電極の刺激が顔面神経へ伝達されてしまう場合があり，その場合，音入力に対して顔面が痙攣することがおこりうる．通常電極の刺激方法を変更することで対応が可能であるが，時には不快感から人工内耳装用ができなくなることもある．

人工内耳の問題点

人工内耳は原理からも分かるとおり内耳障害による高度難聴に対してのみ有効である．聴神経腫瘍をはじめとした後迷路性難聴に対しては効果がない．また，失聴期間が長期に及ぶ場合，内耳性難聴であってもらせん神経節の変性が進むといわれ，その効果は限定的となる．人工内耳は術後すぐに言葉が話せると誤解されていることもあるが，術後，電極ごとに電流量・刺激方法の調整(マッピング)と(リ)ハビリテーションを行って初めて口話コミュニケーションが可能となってくる．特に，言語獲得期以前の失聴者の場合，言語獲得のための継続的なハビリテーションが不可欠であり，その環境整備ができなければ人工内耳の効果は十分望めないものと考えた方がよい．さらに，言語獲得には一般に臨界期というものが存在する(4〜5歳)といわれ[5]，これを過ぎた場合では手術を行ったとしても環境音の認知は可能となりうるが，言語獲得はできない．それゆえ，先天性高度難聴患者の早期発見および早期診断が重要な問題として取り上げられ，新生児スクリーニング・乳幼児健診による難聴児の早期発見・早期療育が取り組まれているが，地域によっても格差が存在しまだ完全とはいえない状況である．なお，先天聾の成人患者に対しては，上記理由により基本的に人工内耳の適応はない．

人工内耳の装用効果は静寂下では語音聴取検査において正答率80%以上も可能であるが，騒音下における聴取は正常者に比べて極めて不良である．学校・会議中・街中をはじめとして，われわれの暮らす環境では騒音下での聴取が必要となる場所が多々あり，この点は今後改善されるべき問題として残っている．

最近の統計で人工内耳装用者の約5～10％程度が機器の故障(外傷含む)，感染などにより摘出・再手術を余儀なくされるという報告がある[6]．機器に起因する故障は各メーカーの取り組みでその率は年々少なくなっているが，感染・外傷などについては一定の率で発生する．特に小児は再手術により言語発達のブランクが生ずるので注意が必要である．

将来展望

各メーカーはディバイスの改良で故障率を少なくするよう努力している．MEL-EL社がホームページ上で報告している故障率は現行機種では6年間累積で純粋な機械トラブルが0.3%程度，外傷などの事故を含めると3.6%程度である．人工内耳の歴史はまだ浅く，長期的な成績については今後分かってくるものと思われ，特に外傷などの外的衝撃に起因する故障率も含めた安全性の向上には一層の注力が期待される．また，コード化法についても今後更なる進展が期待されよう．電極数はお互いの干渉の問題などもあり，単純に数を増やすことには限界があるようである．代わりに擬似的にチャンネル数を増加させるような試み[7]も行われている．また，低周波数について時間的情報も盛り込んでゆくという刺激方法(FSP：Fine Structure Processing)も登場[8]し，今後，言語聴取のみならず音楽などの聞き取り向上なども期待される．

本邦ではまだ保険適用にはなっていないが，海外では人工内耳を両側に適応することが既に始まっている．両側人工内耳の利点としては騒音下での聴取能の改善，音に対する方向感の獲得などがいわれている．コストベネフィットの問題，両側人工内耳を行うことで感染などのリスクが両側になる問題，再生医療など将来的な新たな治療に対する希望など，両側人工内耳を行ううえでいくつか問題はあるが，特に言語獲得期以前の小児に対しては言語獲得期に最大限の聴取能を獲得することが必要であり，今後適応拡大，普及が望まれるところである．

低音部に残聴がある患者に対して，通常よりも短い電極をより非侵襲的に挿入することで，低音部については補聴器などで補聴を行い，聴力の悪い高音部については人工内耳を活用しようというハイブリッド式(EAS：Electro-Acoustic Stimulation)の人工内耳も海外では実用化されつつある[9]．EASの登場で高音急墜型の感音難聴患者が人工内耳の恩恵を受けることができる可能性が出てきた．しかしながら，挿入後低音部の残聴が失われてしまう症例もあり，内耳機能をより確実に温存できる手術方法，ディバイスの改良が望まれるところである．

むすび

人工内耳は高度難聴者に対してする聴覚補償装置として画期的な成果を上げている．ただし，解決されるべき問題もあり，今後ハード・ソフト両面の進歩，および難聴者，特に小児に対する療育システムなどの発展が期待される．

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