

In this study, the relationship between *GJB2* gene mutation and vestibular dysfunction in adults with CD was investigated to confirm whether or not there are any abnormalities associated with the vestibular function.

Material and methods

Subjects

The subjects in this prospective study included 21 patients with CD and 10 healthy volunteers. The patients were excluded from the study if they were being treated with ototoxic drugs or if they had a cytomegalovirus infection, bacterial meningitis, external and middle ear pathological findings, or other risk factors for inner ear damage. No participants had syndromic deafness due to pigmentary retinopathy, nephropathy, goiter, or any other diseases. Patients with vestibular dysfunction due to head trauma, brain tumor, Meniere's disease, or other conditions were also excluded from the study. All subjects underwent an otoscopic examination and were found to have a normal tympanic membrane. Audiometric testing was performed in a double-walled, sound-treated booth. All patients gave their informed consent in writing and the study was approved by the Ethics Committee of Juntendo University School of Medicine.

Genetic analysis

DNA was extracted from peripheral blood leukocytes of the subjects. The coding region of *GJB2* was amplified by PCR using the primers *GJB2*-2F 5'-GTGTGCATTTCGTCTTTCCAG-3' and *GJB2*-2R 5'-GCGACTGAGCCTTGACA-3'. The PCR products were sequenced using the PCR primers and sequence primers *GJB2*-A 5'-CCACGC-CAGCGCTCCTAGTG-3' and *GJB2*-B 5'-GAA-GATGCTGCTGCTTGTGTAGG-3'. These were visualized using an ABI Prism 310 Analyzer (PE Applied Biosystems, Tokyo, Japan).

Vestibular evoked myogenic potentials

The vestibular evoked myogenic potentials (VEMPs) were measured as described in a previous report [6]. Both sound stimuli of clicks (0.1 ms, 95 dBnHL) and short tone burst (500 Hz; rise/fall time, 1 ms, 95 dBnHL) were presented to each side of the ear through the headphones using a Neuropack evoked-potential recorder (Nihon Kohden Co. Ltd,

Tokyo, Japan). The surface electromyographic activity was recorded with the patient in the supine position from symmetrical sites over the upper half of each sternocleidomastoid (SCM) muscle with a reference electrode on the lateral end of the upper sternum. During recording, the subjects were instructed to lift their head up or to turn the contralateral side to induce hypertonicity of the SCM. Thereafter, the electromyographic signals from the stimulated side of the SCM muscle were amplified.

Caloric test

The caloric test in the current study was performed as described elsewhere [7]. Briefly, 2 ml of ice-water (at 4°C) was irrigated in the external auditory meatus to induce a thermal gradient across the horizontal semi-circular canal of one ear. The duration of horizontal and vertical nystagmus was recorded. The results were compared between the right and left ears.

Statistical analysis

The data are expressed as the mean \pm SD. Statistical analyses were conducted using a non-repeated measures analysis of variance (ANOVA). Significant effects were further analyzed by post hoc multiple comparison tests using the Student-Newman-Keuls test. A value of $p < 0.05$ was considered to indicate statistical significance.

Results

Hearing test

The pure-tone averages of 0.5, 1.0, and 2.0 kHz are shown in Table I. The hearing impairments of CD patients ranged from severe (71–95 dB) to profound (>95 dB). The hearing levels of all controls were at the normal level (<30 dB; data not shown).

Genetic analysis

GJB2 mutations were found in nine CD patients (Table I). All three mutations have been described previously in association with deafness. Among these mutations, 235delC mutation was found in eight patients. One nonsense mutation (Y136X) and one frameshift mutation (176-191del) were also identified. In six patients with a homozygous *GJB2* mutation and one patient with a compound heterozygous

Table I. Results of hearing level, genetic analysis, and vestibular function of subjects with congenital deafness (CD)

Case no.	Hearing level (dB)		Sex	Age (years)	Mutation in <i>GJB2</i>	VEMPs	Caloric test
	Left	Right					
Patients with <i>GJB2</i> -related CD							
1	86	98	M	26	Homo 235delC	Right decreased	Left CP
2	106	108	M	25	Homo 235delC	Right decreased	Normal
3	108	106	M	28	Homo 235delC	Right decreased	Normal
4	108	106	M	37	Homo 235delC	Normal	Right CP
5	100	106	M	32	Homo 235delC	Normal	Right poor/left CP
6	80	91	M	25	Homo 235delC	Normal	Normal
7	115	108	M	25	Y136X/235delC	Normal	Normal
Patients without <i>GJB2</i> -related CD							
8	98	98	F	24		Left decreased	Bilateral CP
9	98	115	M	26		Normal	Bilateral CP
10	97	97	M	20		Normal	Normal
11	111	108	M	31		Normal	Normal
12	100	104	F	34		Normal	Normal
13	98	95	M	21		Normal	Normal
14	91	91	M	24		Normal	Normal
15	99	101	F	26		Normal	Normal
16	99	95	F	23		Normal	Normal
17	80	68	M	27		Normal	Normal
18	96	95	M	27		Normal	Normal
19	85	73	M	23		Normal	Normal
Patients with heterozygous <i>GJB2</i> mutation							
20	73	100	M	25	Hetero 235delC	Normal	Normal
21	97	98	M	25	Hetero 176-191del16	Normal	Normal

CP, canal paresis; Poor, nystagmus was obviously weak.

mutation (case nos 1–7); their profound deafness was thought to be caused by a *GJB2* mutation. No *GJB2* mutation was identified in any of the controls.

Vestibular function

No patients or controls had any subjective symptoms of vertigo. Table I shows the results of the vestibular function in all CD patients. Abnormal responses of VEMPs and the caloric test in CD with a *GJB2*-related mutation were observed in three patients each (case nos 1–5). Three patients with a homozygous *GJB2* mutation showed asymmetrical responses in VEMPs (case nos 1–3). Three patients with a homozygous *GJB2* mutation showed asymmetrical responses in the caloric test (case nos 1, 4, and 5). One of them showed both VEMPs and the caloric test

asymmetrical responses (case no. 1). One patient with a homozygous *GJB2* mutation and one patient with compound heterozygous *GJB2* mutation showed normal responses in both VEMPs and the caloric test (case nos 6 and 7). It is notable that five of the six patients with a homozygous 235delC mutation showed no abnormalities in either test. Two heterozygous patients (case nos 20 and 21) showed normal responses in both tests.

Two CD patients with no *GJB2* mutation exhibited abnormal findings for the vestibular tests (case nos. 8 and 9). One patient showed a unilateral reduction in VEMPs and bilateral canal paresis (case no. 8). Bilateral canal paresis was also observed in another patient (case no. 9).

All the controls with normal hearing showed normal responses in both the VEMPs and the caloric test (data not shown).

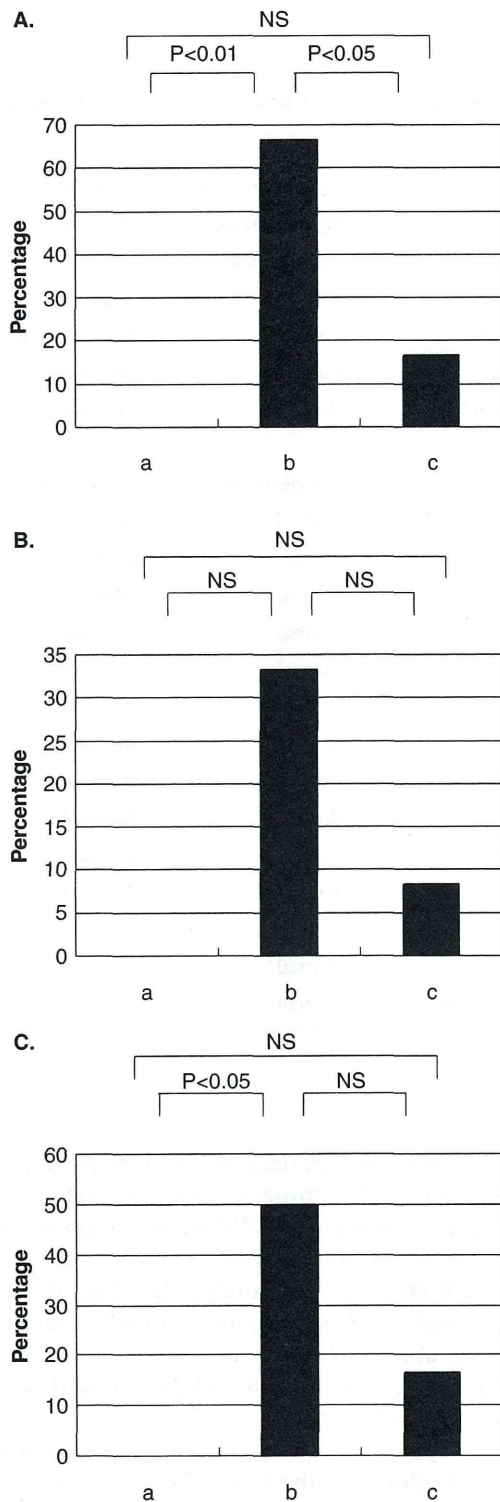


Figure 1. Comparison of the incidence of abnormality in the vestibular tests among the three groups. (A) Percentage showing abnormality in VEMPS and/or caloric test. (B) Percentage showing abnormality in VEMPs. (C) Percentage showing abnormality in the caloric test. a, Controls; b, *GJB2*-related CD subjects; c, CD subjects without *GJB2* mutations.

Statistical analysis of vestibular function in the three groups

Figure 1 shows a comparison of the controls, patients with CD related to a *GJB2* mutation, and those with CD without a *GJB2* mutation. The CD patients with *GJB2* heterozygous mutation were excluded from this statistical analysis, since their symptoms of hearing impairment are not necessarily caused by the *GJB2* mutation alone. Vestibular dysfunction showing an abnormality in VEMP and/or the caloric test significantly increased in patients with *GJB2*-related CD in comparison with those with CD without *GJB2* mutation ($p < 0.05$) and the controls ($p < 0.01$), whereas no difference was observed between CD without a *GJB2* mutation and the controls (Fig. 1A). No differences in the incidence of abnormality in VEMPs were observed among the three groups (Fig. 1B). The incidence of abnormalities in the caloric test in patients with *GJB2*-related CD differed significantly from that in the controls, but the other two comparisons were not significant (Fig. 1C).

Discussion

In this study, vestibular tests were performed in CD patients with or without a *GJB2* mutation by measuring the VEMPs and using the caloric test. Only one report has previously investigated the vestibular function of patients with *GJB2*-related CD [8]. The authors noted that five of the seven patients showed no VEMP responses bilaterally and that only one case had a unilateral pathological response in the caloric test, which led to the conclusion that CD with a *GJB2* mutation is associated with severe saccular dysfunction. However, in the present study, there were no patients showing the absence of both VEMP and a caloric response. Todt et al. [8] showed the existence of *GJB2* mutations that do not cause CD (polymorphisms), thus suggesting a considerable bias. Furthermore, patients with low-grade hearing loss were included in their study. In contrast, all of the *GJB2* mutations detected in the present study are known to cause CD in the Asian population [9]. In addition, the present study included only patients with severe to profound hearing loss, which would therefore clarify the correlation between CD and *GJB2* mutations. Among the seven patients with *GJB2*-related CD, five (71.4%) showed abnormal responses in either or both tests. The incidence was apparently and significantly higher than that in patients with CD without a *GJB2* mutation (2/13: 15.4%). Moreover, the incidence in the controls significantly differed from that in patients with CD related to a *GJB2*

mutation but not in those with CD without *GJB2* mutation. Therefore, these findings support the hypothesis that *GJB2* mutations play a critical role in the disturbance of the vestibular function.

GJB2 mutations cause profound deafness and the associated mechanism has been discussed in several studies [10,11]. A recent study showed that *GJB2* is indispensable in the normal development of the organ of Corti and normal hearing on the basis of the study in *Gjb2* dominant-negative mutant mice [12]. Despite the widespread expression of Cx26 in both the cochlear and vestibular organs [4], the vestibular function impairment of the patients with a *GJB2* mutation is not as severe as the hearing dysfunction observed in the present study. Two hypotheses have been proposed to explain this inconsistency between hearing and balance function. One hypothesis is based on the fact that two temporal bone studies performed in patients with *GJB2*-related hearing impairment in the previous study revealed that one patient had mild vestibular hydrops and saccular degeneration, while another patient had a dysplastic neuroepithelium of the saccule [13,14]. This suggests that a *GJB2* mutation can cause morphological dysplasia in not an entire organ, but in part of the vestibular organs. This is contrast to the cochlea of these patients, which showed nearly total dysplasia of the organ of Corti. These histopathological studies support the results of the vestibular dysfunction of patients with *GJB2*-related CD in the present study. The other hypothesis is based on the presence of several connexins such as Cx26, Cx30 (encoded by *GJB6*), Cx31 (encoded by *GJB3*), and Cx32 (encoded by *GJB1*) in the inner ear. A previous study showed all of these connexins to be distributed in the vestibular organs [15]. Cx30 gene knockout mice had hair cell loss in the saccule, which was restored by the over-expression of the Cx26 gene [16]. Therefore, the specific loss of Cx30 causes vestibular dysfunction, which can be compensated by other types of connexins. The present clinical study in which a complete defect of Cx26 resulted in a definitive but partial dysfunction of vestibular end organs can be explained by the compensation of other connexins normally expressed in the vestibule. Further studies are required to clarify the relationship between connexins and the vestibular function.

Although there was a statistically significant difference in the objective examination of the vestibular function among patients with *GJB2*-related CD, those with CD without a *GJB2* mutation, and healthy controls, none of these subjects had any vestibular symptoms regardless of the presence or absence of a *GJB2* mutation. The peripheral

vestibular dysfunction predicted in individuals with the *GJB2* mutation may be compensated by the central vestibular system in young patients with deafness, as shown in the present study. However, aging is known to affect both the peripheral and central vestibular system [17]. In patients with a *GJB2* mutation, the vestibular symptoms may progress with aging. Another problematic point regarding patients with CD related to *GJB2* mutations is cochlear implantation, which has been reported to cause vestibular dysfunction, such as a reduction of the caloric responses [18] and a decrease in the VEMP responses [19]. It is thought that the mechanical damage caused by the insertion of the electrode may induce vestibular dysfunction [20]. In the present study, four patients with *GJB2*-related deafness showed unilateral vestibular dysfunction, while only one of them had bilateral dysfunction. Therefore, it should be emphasized that the assessment of the vestibular function in patients with *GJB2*-related CD is important to determine which side of the ear should be selected to insert the cochlear implant.

Conclusions

A *GJB2* mutation is responsible not only for deafness but also for vestibular dysfunction. However, such vestibular dysfunction is likely to be unilateral and less severe in patients with a *GJB2* mutation than in those with bilateral deafness.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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実験動物を用いた内耳細胞治療研究へのアプローチ

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Experimental Approaches to Inner Ear Cell Therapy Using Laboratory Animals

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Recently, a number of clinical studies on cell therapy have been reported and used in clinical practice for several intractable diseases. Inner ear cell therapy for sensorineural hearing loss also has been studied using some laboratory animals, although to date reports on successful hearing recovery have been few.

Previously, we developed a novel rat model of acute sensorineural hearing loss due to fibrocyte dysfunction induced by a mitochondrial toxin and performed cell therapy with bone marrow mesenchymal stem cells (MSCs). In this study, we injected MSCs into the lateral semicircular canal; a number of these stem cells were then detected in the injured area in the lateral wall. Rats with transplanted MSCs in the lateral wall demonstrated a significantly higher hearing recovery ratio than the untreated controls. These results suggested that mesenchymal stem cell transplantation into the inner ear may be a promising therapy for patients with sensorineural hearing loss due to degeneration of cochlear fibrocytes.

In this article, we review studies on inner ear cell therapy using some laboratory animals including rodents such as mice and rats, and primates such as cynomolgus monkeys (*Macaca fascicularis*).

Key words : inner ear, cell therapy, sensoryneural hearing loss, stem cell

はじめに

感音性難聴の原因は多岐にわたるが、近年の遺伝子改変動物開発技術の向上や多種のモデル動物の開発により多くの病態メカニズムが解明に近づいている。すべての先天性疾患の中でも頻度の高い遺伝性難聴においては、難聴家系や突然変異難聴マウスの遺伝子解析によって多くの遺伝性難聴原因遺伝子が同定されている。初期に発見された遺伝性難聴の原因の多くは内耳有毛細胞の変性または機能的・形態的異常であったため、多くの研究者が有毛細胞を中心に難聴の病態メカニズム解明に取り組んできた。哺乳類の有毛細胞は再生能力を持たないため遺伝子導入などによる有毛細胞再生の誘導も盛んに研究されてきた^{1,2)}。その一方で内耳への細胞移植による有毛細胞の修復の試みも行われているが、特殊なリンパ液で満たされた内耳の構造的特徴から、聴力を保持しつつ標的部位に移植細胞を到達させ分化させることは容易では

ない。そのため有毛細胞の修復には多種のモデル動物を用いた多くの検討実験が必要と考えられる。近年有毛細胞以外にも蝸牛線維細胞などの機能異常が単独で難聴病態の引き金となることも明らかとなっており、多様な治療戦略が求められている。幹細胞の損傷部への移動能力や組織環境（ニッチェ, niche）による分化誘導を十分に検討すれば細胞治療は内耳組織変性に対する治療にも応用可能と考えられる。著者らの報告では実験的に蝸牛線維細胞のみに傷害を与えたラットへ半規管外リンパ液を経由した細胞液還流法を用いることにより、損傷部の修復と聴力回復率を高めることに成功した³⁾。現在はヒト疾患に近い遺伝性難聴モデル動物への各種の幹細胞移植に取り組んでいる。また、サル類を用いた細胞移植アプローチの検討も今後応用性を高めるためには非常に重要であるため現在、カニクイザルによる検討を行っている。各種のモデル動物の特徴を考慮した細胞移植実験検討を

積み重ねることにより、将来的には有毛細胞も標的とした多様な難聴に対する聴力回復も不可能ではないと考えられる。本稿では各種実験動物を用いた内耳への細胞治療に関する知見について報告する。

内耳細胞治療実験に用いられる実験動物

外傷、騒音、感染、薬物障害、血流障害、加齢に起因する聴覚障害動物モデルは多く開発されており、細胞治療研究のための有用な実験モデルとして活用することができる。著者らはミトコンドリア阻害薬を用いて蝸牛線維細胞のみに損傷を与えるモデルラットを開発し、この細胞移植実験に成功している。しかしこのような実験的に内耳損傷を誘導した動物モデルがヒトと同等な内耳組織障害および機能的障害を忠実に再現しているかという点に関しては実証することは困難である。これに対し原因タンパク質がすでに特定されている遺伝子改変動物または突然変異動物はヒト遺伝性難聴の病態の多くが一致していると考えられる。細胞移植によりそのタンパク質が担う機能を回復させることができれば、幹細胞が正常に分化し失われていたタンパク質機能を取り戻した結果として聴力が回復したことを実証しやすい。有毛細胞の変性が顕著にみられるモデル動物としては、アッシャー症候群原因遺伝子 (Pcdh15⁴, Cdh23⁵, Sans⁶, Harmonin⁷, Myosin VIIa⁸) など) の突然変異動物あるいは遺伝子改変動物が、明白な表現型を持つため有毛細胞の研究に広く用いられている。これらの進行性の組織変性は重度であり有毛細胞の変性から連鎖的にラセン神経節細胞の消失へとつながる場合も多い。そのため細胞治療による細胞の生着・分化の検討は可能であるが聴力改善の検討は現段階で容易ではないと思われる。蝸牛線維細胞を標的とした場合、有毛細胞変性を伴わず蝸牛線維細胞のみに変性を持つ Brn4 欠損マウス⁹、Otospiralin 欠損マウス¹⁰ が有効であると考えられる。これらの聴力改善の可能性は有毛細胞を標的とした細胞治療より格段に高いと思われる。ヒト遺伝性難聴でもっとも高頻度に出現するコネクシン26の遺伝子欠損マウスおよび優性阻害トランスジェニックマウス¹¹ は同遺伝子が蝸牛線維細胞および支持細胞に主に発現するため、著者らの行った骨髄間葉系幹細胞移植も有効であると考えられる。

蝸牛線維細胞を標的とした骨髄間葉系幹細胞移植

蝸牛ラセン靭帯およびラセン板縁を構成する蝸牛線維

細胞はナトリウムポンプとギャップジャンクションによる蝸牛内イオンの能動輸送および受動輸送という単純な機能を担っている。しかしながら蝸牛線維細胞の傷害は複数の先天性および後天性難聴の主要因となることが示され、その重要性が近年示唆されている。とくにヒト非症候性難聴 DFN3 の原因因子 Brn4 の遺伝子欠損マウス⁹ や otospiralin 欠損マウス¹⁰ では蝸牛線維細胞の変性を主要因とした聴力低下が実証され、有毛細胞を含むコルチ器と同様に正常聴力を維持するうえで重要性の高い細胞群であることが明確に示された。また複数の加齢性難聴モデル動物においても蝸牛線維細胞の変性が他の細胞に先立ち開始することが報告されている^{12)~14)}。また蝸牛線維細胞は単一細胞としての機能が単純であるにもかかわらず内耳機能における重要性が高いという点から、高度に分化した有毛細胞に比べて細胞治療が成功する可能性が格段に高いと考えられる。これらのことから蝸牛線維細胞は多種の感音難聴に対する新規治療法確立への重要な標的となりうると考えられる。著者らは薬剤

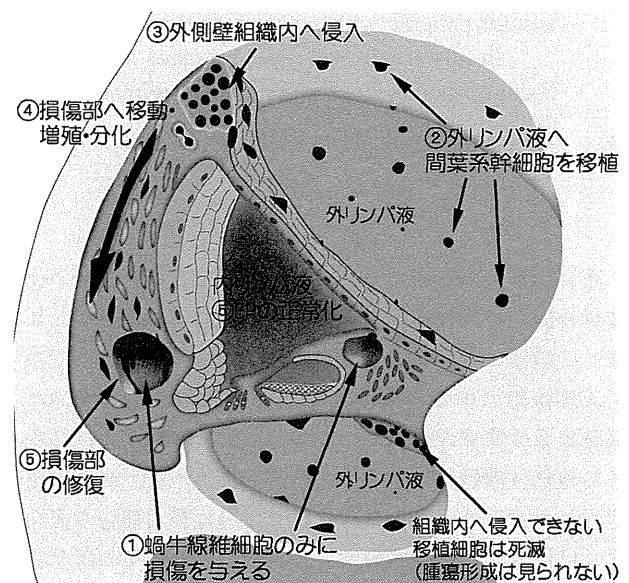


図1 蝸牛線維細胞をターゲットとした骨髄間葉系幹細胞移植での損傷部の修復および推測された移植細胞の移動経路。薬剤投与によりラセン靭帯およびラセン板縁に選択的に損傷を与え①、その後外リンパ液へ骨髄から採取した間葉系幹細胞を半規管からの還流により投与②した結果、投与した間葉系幹細胞が外側壁組織内へ進入し④、移動・増殖・分化④により損傷部の修復⑤を促進し高周波数音域の聴力回復率が有意に上昇した。(Reprinted from Am J Pathol Am J Pathol 2007, 171 : 214 ~ 226 with permission from the American Society For Investigative Pathology)

局所投与により蝸牛線維細胞の二点にのみ限局的なアポトーシスを起こすモデルラットを開発し¹⁵⁾¹⁶⁾、半規管からの骨髓間葉系幹細胞の外リンパ液還流投与を行った。その結果、移植 11 日後の高音域 (40 KHz) の聴力回復が有意に促進し、外側壁の蝸牛線維細胞損傷部に多数の移植細胞が観察された。組織内には腫瘍化を示す移植細胞は観察されなかった。移植細胞は蝸牛外側壁の頂回転側、外リンパ液に面している部分で多くみられ、この部位を中心に蝸牛組織に侵入し損傷部まで移動したと考えられる。損傷部ではコネクシンの発現とともに隣接細胞と接合する移植細胞が観察され、イオン輸送経路の回復による内リンパ液 K^+ 濃度の正常化が聴力回復に寄与したと推測される (図 1)³⁾。

内耳への細胞投与法

著者らの初期の移植検討実験では、ラット蝸牛管付近より細胞液投与を試みた際はどの部位でも手術による永続的な聴力低下がみられ、蝸牛組織には繊維化が認められた。著者らは Iguchi らの方法¹⁷⁾を参考にラットの後半規管および外側半規管にそれぞれ小孔を開け、片側から微小チューブを挿入し細胞液 (1×10^5 cells/20 μ l) での 10 分間の還流を行った。この方法では手術による聴力低下はほとんどみられず、大量の細胞を蝸牛内に導入することができるため内耳細胞治療に適した投与方法であると思

われる。また新生児難聴スクリーニング直後の早期治療を想定した内耳への投与方法として、Iizuka ら¹⁸⁾は生後 0 日齢の幼若マウスへ微小ガラス管を用いて遺伝子治療用ウイルス液を非侵襲的に外リンパ液内へ注入することに成功している。同方法は非侵襲性を必要とする幼若個体への細胞注入にも応用可能であると考えられる。この方法では外リンパ液の漏出がほとんどないため、少量であれば非侵襲的に細胞液を注入することができる。細胞移植用としてはガラス管先端の直径をパッチクランプ用のプレーで微調整することで利用可能と考えられる。

サル類を用いた細胞治療研究の重要性

げっ歯類を用いることにより、新規な細胞治療法の開発や多くの分子生物学的、生理学的データの取得が期待できる。一方でげっ歯類ではその生理・代謝機能が必ずしもヒトを忠実に反映していない部分もあり、ヒトへの外挿面で必ずしも一致した効果を得られない可能性も考えられる。たとえばヒトと同様サル類でも出生直後に外部の音刺激を入力することができると考えられるが、マウスやラットでは生後約 10 日齢までは内耳が未成熟であるため音の入力が開始しない。新生児難聴スクリーニング直後の細胞治療を目的とした検討の場合などはとくに成熟レベルによる細胞治療の有効性や安全性が大きく異なることが予想されるため、実験用サルによる安全性・

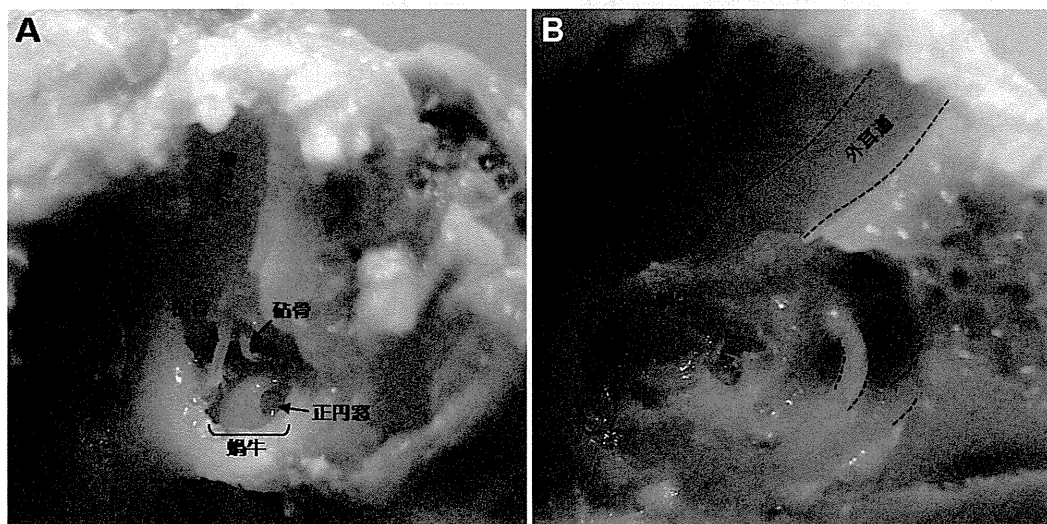


図 2 成熟カニクイザルの内耳

A. 上顎側より削開し外耳道、耳小骨、蝸牛を露出した。

B. さらに内耳周囲を削開し蝸牛内部および半規管を露出した。ヒトとほぼ同様の内耳構造およびその周囲構造がみられる。

有効性の評価が将来的に非常に重要になると考えられる。マウスやラットで開発された細胞治療法を臨床応用へ近づけるためには、サル類（カニクイザル等）を用い、それらの安全性評価データをヒトへ外挿する必要がある。サル類を用いた細胞治療実験では、マウスやラットによる基礎データをもとに有効かつ安全な移植方法や移植細胞の種類、成熟ステージを評価することが重要であると考えられる。現在、カニクイザル頭部を用いた細胞治療アプローチに関する検討実験を行っている（図2）。カニクイザル側頭骨は手術の際に削開を進める角度などがヒトと多少異なるが、内耳構造やその周囲構造に共通点が多く細胞移植手術による半規管や正円窓へのアプローチもヒトのモデルとして非常に有効であると考えられる。

各種実験動物の特徴

マウスに関していえば、近年膨大な種類の遺伝子改変マウスが各国でされ、データベース化や共有研究資料として分配されているものもある。病態変化や細胞移植後の変化を分子生物学的手法により解析する場合は情報や各種実験ツールの多さからマウスが他の実験動物と比較し圧倒的に有用性・汎用性が高いと考えられる。各種幹細胞の入手もマウスでは比較的容易である。しかし内耳への細胞の局所投与を必要とする場合はアプローチの方法やターゲットとする疾患に対し最適な病態モデルを得るため、マウス以外のげっ歯類（モルモット、スナネズミ、ラット）も十分有効に活用できる。半規管経由の細胞移植に関していえば、げっ歯類では外側半規管および後半規管が側頭骨表面に露出しているためアプローチが容易である。

サル類に関していえば、研究コスト面での負担が大きい臨床応用へ向けての安全性・有効性評価の面で必須の実験動物といえる。カニクイザル (*Macaca fascicularis*) は我が国でも保有する施設が多数存在し、多くの動物実験に利用されている。前述したように内耳周辺の組織構造、生理機能がヒトとほぼ同等と考えられるため、げっ歯類で有効性が実証された細胞治療法をカニクイザルにおいて有効性及び安全性を再評価することが臨床応用に向けて重要であると考えられる。

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