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Model Experiment of Benign Paroxysmal Positional Vertigo Mechanism Using the Whole Membranous Labyrinth

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Whole membranous labyrinths of bullfrogs were used in order to replicate the human vestibule. The posterior semicircular canals (PSCs) were exposed, leaving the remaining membranous labyrinth encapsulated in the otic capsule. Vibration was applied to the surface of the bony capsule using a conventional surgical drill in order to dislodge the otoconia from the utricle. The position of the preparation was controlled so that the dislodged otoconia were attached to the cupular surface. This was regarded as a cupulolithiasis model. The action potentials changed instantaneously according to the gravitational force on the cupula. When the otoconia were dislodged and held within the PSC lumen, the position of the whole preparation was changed so that the otoconia moved back and forth within the canal lumen. This is a model of canalolithiasis. The action potentials changed in combination with the otoconial movement after a latent period. Both cupulolithiasis and canalolithasis are potentially valid mechanisms of benign paroxysmal positional vertigo (BPPV). However, canalolithiasis is the most likely mechanism of BPPV, which is usually characterized by nystagmus of short duration and long latency. A vibratory stimulus was able to detach the otoconia from the utricle, suggesting that mechanical insult could be a possible etiology of BPPV. *Key words: benign paroxysmal positional vertigo, canalolithiasis, membranous labyrinth, otoconia.*

INTRODUCTION

Although benign paroxysmal positional vertigo (BPPV) is a common vestibular disorder, its etiology has not been fully elucidated. Cupulolithiasis, as proposed by Schuknecht (1), as well as canalolithiasis, as proposed by Hall et al. (2), Brandt and Steddin (3) and Epley (4), have been considered to be possible mechanisms. Suzuki et al. (5), using the isolated frog posterior semicircular canal (PSC), demonstrated that canalolithiasis represents the most valid mechanism of BPPV. However, the question remains as to whether or not the otoconia move and effectively stimulate sensory cells within the intact canal. Whether or not mechanical stimulation, such as vibration, could dislodge the otoconia is another question. In this study, models of the whole membranous labyrinth were used in order to replicate the physiological condition of the vestibule.

MATERIAL AND METHODS

Fourteen bullfrogs (Rana catesbeiana) were used. They were deeply anesthetized with ether and then decapitated. The bony labyrinth was removed en bloc. The caudal bony capsule was chiseled so that the entire PSC was exposed. The bone covering the vestibular nerve trunk and superior and inferior nerve branches was also removed. The remaining membranous labyrinth was left encapsulated in the bony capsule. Vibration was applied to the surface of the bony capsule using a conventional surgical drill for 15 min in order to dislodge the otoconia from the utricle (Fig. 1). Care was taken not to disturb the other parts of the labyrinth. The inferior vestibular nerve was separated from the main vestibular nerve bundle and was sucked into a glass suction electrode to record PSC compound action potentials (CAPs).

CAPs were recorded for two positions of the PSC. The position with the cupula-to-crista axis in the horizontal plane and the utricular side upwards was designated the "canal-down" position. The position with the utricular side of the PSC placed downwards and the canal side upwards was designated the "canal-up" position. The PSC was placed in these two positions from the position with the cupula–crista plane in the vertical plane (neutral position) at the approximate speed used in the positioning nystagmus test. The positional change was achieved by manually controlling the forceps that firmly held the entire preparation. Successful positional changes required a great deal of practice and technical skill, as the inferior vestibular nerve had to be securely sucked into the glass suction electrode throughout the procedure.

In the first experiment (Experiment 1a), the position of the preparation was controlled so that the dislodged otoconia were fixed onto the cupular surface. This is a model of cupulolithiasis (Fig. 2). In the second experiment (Experiment 2a), the dislodged otoconia were held within the canal lumen. In order to let the otoconia move a long distance, they were first allowed to accumulate near the crista and the PSC was quickly turned "canal-down", thus producing ampullofugal movement of the otoconia. Sec-

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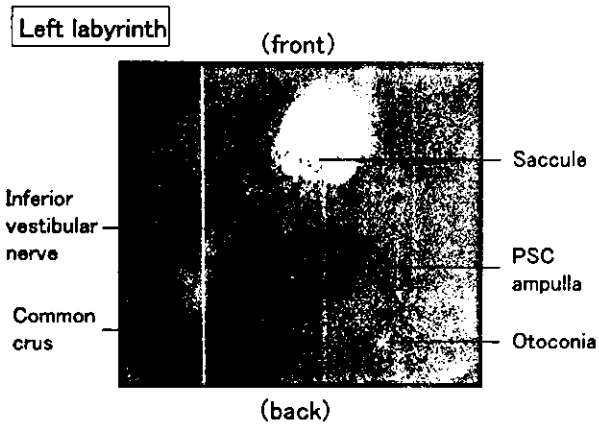

Fig. 1. View of the entire preparation.

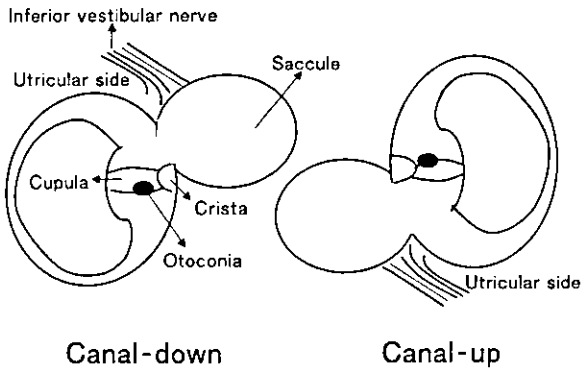

Fig. 2. Details of Experiment 1 (model of cupulolithiasis).

ondly, the otoconia were allowed to accumulate in the canal far away from the crista and then the PSC was turned "canal-up", thus producing ampullopetal movement. This is a model of canalolithiasis (Fig. 3).

Next, we created cupulolithiasis and canalolithiasis models using an easier method. The membranous labyrinth was carefully cut by 0.5 mm at the crus commune to create a tiny opening. A small piece of otoconia removed from the sacculus of the other ear was introduced through this opening into the canal lumen in order to mimic the conditions of Experiments 1a and 2a. These are designated Experiments 1b and 2b.

RESULTS

After 15 min of drilling, the otoconia were dislodged and moved into the PSC lumen in approximately half of the preparations. In the other preparations, no otoconia were found in the PSC lumen. The preparations with the otoconia dislodged into the PSC were used for the present study.

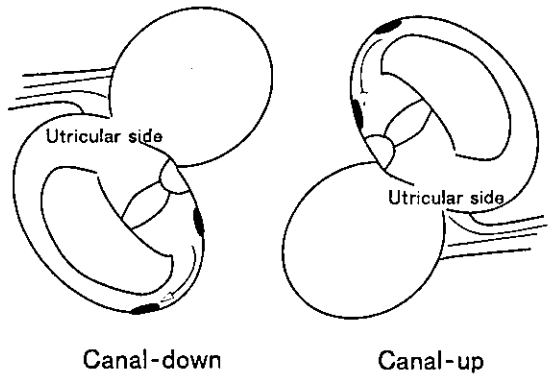

Fig. 3. Details of Experiment 2 (model of canalolithiasis).

Experiment 1. Model of cupulolithiasis

Seven frogs were used. When the PSC was placed in the "canal-down" position, remarkable CAPs were evoked (Fig. 4). In Experiment 1a (intact membranous labyrinth; $n = 3$), the mean latency ($\pm$ SD) was 1.8 ± 0.2 s. The responses were sustained for a long time, resulting in a decremental time constant > 43 s. When the PSC was placed in the "canal-up" position, the discharges were markedly inhibited (Fig. 4). In Experiment 1b (otoconia inserted through the membranous opening; $n = 4$), the mean latency was 1.8 ± 0.3 s. The time constants were > 36 s and thus comparable with those observed in Experiment 1a.

Experiment 2. Model of canalolithiasis

Seven frogs were used. In the "canal-down" position, in which the otoconia moved towards the canal side, the spikes increased after a significant latency (Fig. 5). In Experiment 2a (intact membranous labyrinth; $n = 3$), the mean latency was 3.5 ± 0.4 s, i.e. longer than that observed in Experiment 1. The mean decre-

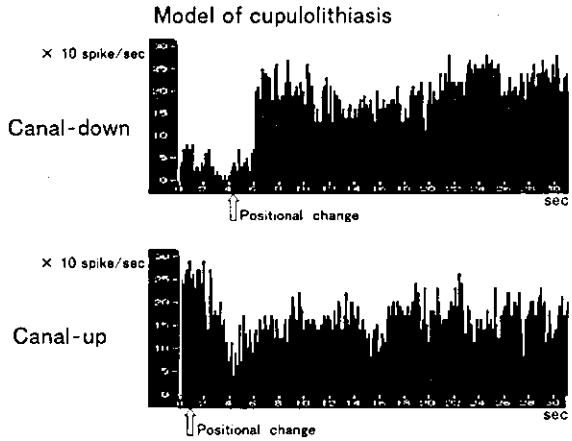

Fig. 4. Example of spike density histograms of the CAPs evoked in Experiment 1a. Note that these responses are the least adaptive.

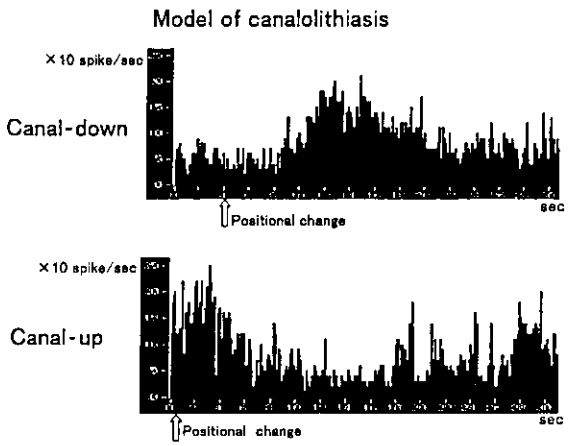

Fig. 5. Example of spike density histograms of the CAPs evoked in Experiment 2a. Note that the responses are adaptive.

mental time constant was 6.8 ± 1.0 s, which was shorter than that observed in Experiment 1. When the otoconia moved towards the crista in the "canal-up" position, the discharges were inhibited after a similar latency (Fig. 5). In Experiment 2b (otoconia inserted through the membranous opening; $n = 4$), the mean latency was 4.0 ± 0.7s and the mean time constant 8.25 ± 0.6 s, values comparable with those observed in Experiment 2a.

DISCUSSION

Although BPPV is a common vestibular disorder, its etiology has not been fully elucidated. Cupulolithiasis (1) and canalolithiasis (2–4) have been regarded as possible candidate mechanisms. In a previous study, Suzuki et al. (5) confirmed the physiological validity of both mechanisms, but canalolithiasis best fits for the clinical features of BPPV, in terms of latency, rise time and time constant of the evoked response. The exact nature and origin of the cupular deposit and floating substance have not been determined (1, 6, 7). These substances possibly have their origins in detached or degenerated otoconia (1, 3, 4). However, questions remain as to whether or not the otoconia move and effectively stimulate sensory cells within the intact canal and whether mechanical stimulation, such as vibration, could dislodge the otoconia.

In this study, the whole membranous labyrinth was used in order to replicate the human vestibule. It was possible to dislodge the otoconia from the utricle using the vibration of a surgical drill and move them into the PSC. It was also possible to attach the otoconia to the cupula. These results suggest that detachment of the otoconia after head trauma could represent an etiology of BPPV. Whether or not there are any causal factors that facilitate otoconial detachment should be further studied. We suspect that aging, circulation disorders or labyrinthitis may be involved.

As shown in Experiment 1, changing the position of the PSC from the neutral plane instantaneously affects the neural discharge. The pattern of discharge changes was either excitatory or inhibitory in accordance with the gravitational force on the cupula. When the preparation was in the "canal-down" position, the response was excitatory, and in the "canal-up" position, it was inhibitory. This response pattern is the same as that resulting from conventional mechanical endolymphatic flow (8). The results of Experiment 1b were comparable to those of Experiment 1a, suggesting that a mixture of endolymph and Ringer' solution does not affect the physiological effect of cupulolithiasis.

In Experiment 2, characteristic movement of the otoconia was observed. They invariably moved as a compact mass and slid along the canal wall. When the otoconia moved inside the canal, the neural discharges changed according to the direction of the movement. There was also a latent period before the discharge change occurred. It was observed that the otoconia initially moved slowly and then accelerated upon a positional change. The frictional force between the otoconia and the canal wall is responsible for otoconial movement and latency beginning slowly. The results of Experiment 2b were comparable to those of Experiment 2a, suggesting that a mixture of endolymph and Ringer's solution does not affect otoconial movement.

The present experiments demonstrate that both cupulolithiasis and canalolithiasis effectively stimulate the cupula and are thus potential mechanisms of BPPV. Typical BPPV is characterized clinically by brisk and rotatory-dominant nystagmus with a latency of several seconds and a short duration. This feature could be explained better by the mechanism of canalolithiasis. However, there is another type of positional vertigo with similar rotatory nystagmus but with negligible latency and a longer duration (more than several minutes). This type of vertigo can be explained by the mechanism of cupulolithiasis.

CONCLUSIONS

A vibratory stimulus was shown to detach the otoconia from the utricle, suggesting that mechanical insult is a possible etiology of BPPV. The time constant was shorter and the latency longer in canalolithiasis, a result comparable with that obtained in our previous study using the isolated canal (5). Canalolithiasis represents the best potential mechanism of BPPV,

which usually shows nystagmus with a short duration and long latency.

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Experimental Study of Speed-dependent Positional Nystagmus in Benign Paroxysmal Positional Vertigo

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Furuya M, Suzuki M, Sato H. *Experimental study of speed-dependent positional nystagmus in benign paroxysmal positional vertigo*. Acta Otolaryngol 2003; 123: 709–712.

Objective—One of the clinical characteristics of benign paroxysmal positional vertigo (BPPV) is that the more quickly the head position changes, the more severe the vertigo. This suggests that the velocity of the head change is critical in determining the occurrence and severity of vertigo. The aim of this study was to examine factors determining the symptoms of BPPV using models of canalolithiasis and cupulolithiasis.

Material and Methods—Canalolithiasis and cupulolithiasis models were prepared using the bullfrog posterior semicircular canal (PSC). The ampullary nerve discharges were compared between quick and slow positional changes to examine factors determining the symptoms of BPPV.

Results—In the canalolithiasis model, the acceleration of the otoconia was greater for the quick positional change. This resulted in a greater discharge with a longer duration. With the slow positional change, the discharges were smaller and shorter. In the cupulolithiasis model, the discharges were sustained and their magnitude did not differ between the quick and slow positional changes. The canalolithiasis model influenced the magnitude of discharge of the PSC depending on the speed of the positional change.

Conclusion—Canalolithiasis is the more likely mechanism of BPPV, which is characterized by various degrees of vertigo upon kinetic positional change. *Key words: canalolithiasis, cupulolithiasis, isolated semicircular canal, otoconia, positional vertigo.*

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is a common vestibular disorder. It was first reported by Bárány (1) in 1921, and the concept of its pathology was proposed by Dix and Hallpike (2) in 1952. BPPV is known to be caused mainly by canalolithiasis or cupulolithiasis (3) of the posterior semicircular canal (PSC) (4–6). In model studies using bullfrogs, Suzuki et al. (7) showed that the sensory cells could be effectively stimulated by the moving otoconia within the PSC and proposed canalolithiasis to be the most likely mechanism of BPPV.

One of the clinical characteristics of BPPV is that the more quickly the head position changes, the more severe the vertigo. As a result, BPPV patients tend to slowly change their head position in order to avoid vertigo. This suggests that the velocity of the head change is critical in determining the occurrence and severity of vertigo. In this study, we prepared models of canalolithiasis and cupulolithiasis using the bullfrog PSC. The ampullary nerve discharges were compared between quick and slow positional changes to examine factors determining the symptoms of BPPV.

MATERIAL AND METHODS

Thirty bullfrogs weighing 130–150 g were used. The PSC was isolated, together with the ampullary nerve, in Ringer's solution according to a previously reported method (7). A small mass of the otoconia was removed from the sacculus using a fine forceps. Canalolithiasis models were prepared by inserting the saccular otoconia through the open end of the canal (Fig. 1). Cupulolithiasis models were prepared by placing the otoconia on the cupula surface (Fig. 1). In total, 18 canalolithiasis and 12 cupulolithiasis models were created.

The PSC was manipulated in order to alter its position in the vertical plane. In the canalolithiasis model, the canal was placed downwards (canal down; C-D), so that the otoconia moved in the ampullofugal direction (Fig. 1). When the canal was directed upwards (canal up; C-U), the otoconia moved in the ampullopetal direction (Fig. 1). In the cupulolithiasis model, the canal was also placed in either C-D or C-U positions (Fig. 1). In the C-D position, the cupula was depressed towards the ampullofugal direction and in the C-U position it was depressed towards the ampullopetal direction. The time allowed for the positional change was set at either 1 s, designated "quick change", or 10 s, designated "slow change".

A metronome was used to time the positional change of the PSC. Whilst listening to the metronome counting seconds, the position of the PSC was changed by manual handling of the forceps holding both edges of the PSC, so that the whole process of positional change took either 1 or 10 s. As a consequence, the quick positional change (1 s) produced a greater acceleration and the slow change (10 s) a much smaller acceleration of the otoconia. Successful positional changes required a great deal of technical skill and practice, as the PSC nerve had to

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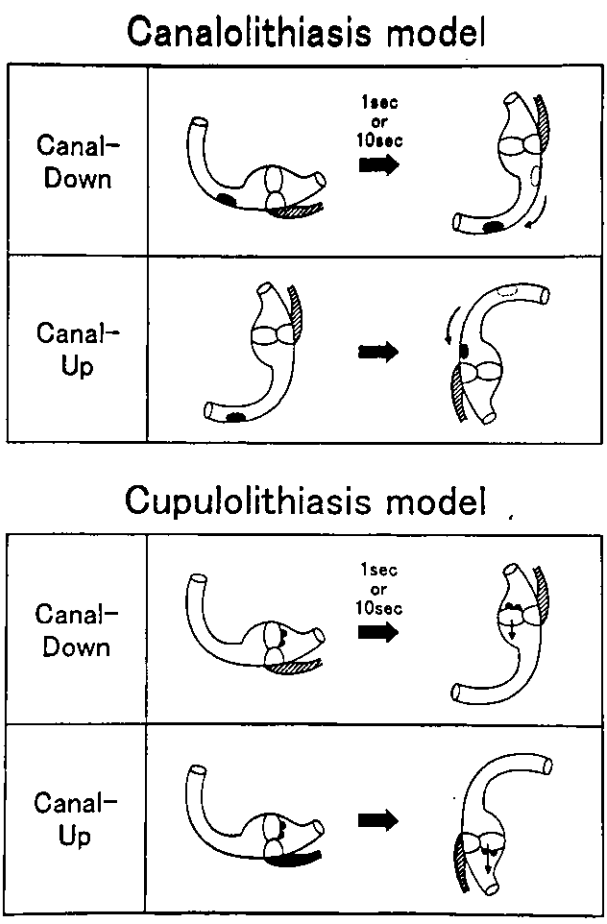

Fig. 1. Schema of the models of canalolithiasis and cupulolithiasis. Black dots represent the otoconial mass. In the canalolithiasis model, the otoconia are within the canal. By changing their position, the otoconia move as indicated by the arrows. In the cupulolithiasis model, the otoconia are on the cupula surface. By changing their position, the otoconia depress the cupula as indicated by the arrows.

be securely sucked into the glass suction electrode throughout the procedure.

The ampullary nerve discharges elicited by the positional changes were recorded using the glass suction electrode (Fig. 2). The discharges were converted into a spike density histogram. The maximum spike counts, the response duration and the latencies to the response onset and to the peak were compared between the quick and slow positional changes.

RESULTS

In the canalolithiasis model, the ampullary nerve discharges increased in magnitude when the otoconia moved in the ampullofugal direction in the C-D position. They decreased in magnitude when the otoconia moved in the ampullopetal direction in the C-U position. The excitatory discharges evoked in the C-D position were used for analysis. The means

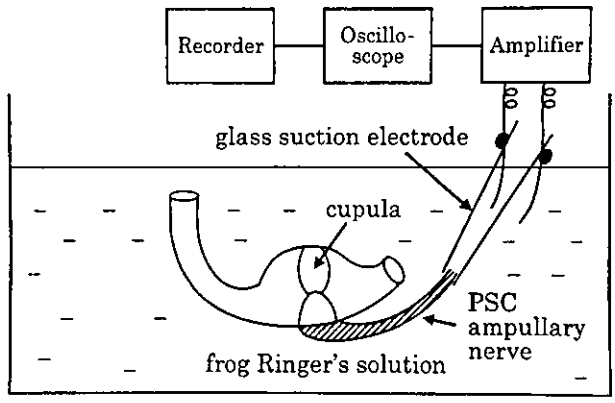

Fig. 2. Schema of the system for recording ampullary nerve compound action potentials.

(±SDs) of the maximum spike counts were 286.3± 9.3/s for the quick and 239.6±26.7/s for the slow positional change and this difference was significant ($p < 0.01$). The mean response durations were 19.8± 7.5 s for the quick and 13.8±1.7 s for the slow change and this difference was significant ($p < 0.01$). The mean latencies to the onset were 1.8±0.5 s for the quick and 5.6±0.9 s for the slow change and this difference was significant ($p < 0.01$). The mean latencies to the peak were 5.1±1.4 s for the quick and 11.2±4.2 s for the slow change and this difference was significant ($p < 0.01$). In the canalolithiasis model, the quick positional change resulted in greater and longer neural discharges, with a shorter latency (Figs. 3 and 4).

In the cupulolithiasis model, the ampullary nerve discharges increased in magnitude when the otoconia were placed on the cupula in the C-D position. The discharge decreased in magnitude in the C-U position. The excitatory discharges were used for analysis. In the C-D position, the averaged maximum spike counts

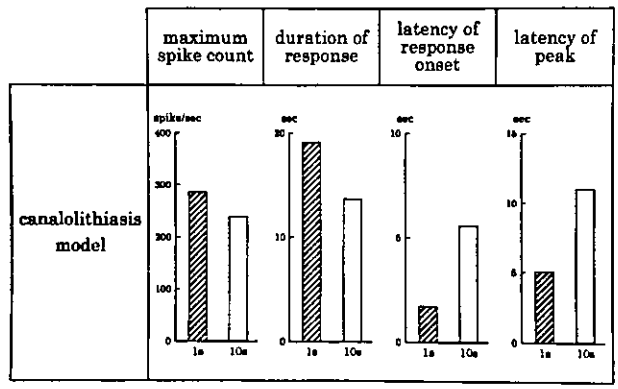

Fig. 3. The means of maximum spike count, duration of response, latency of response onset and latency of peak in the canalolithiasis model. Hatched bars: values for 1-s positional change. Open bars: values for 10-s positional change.

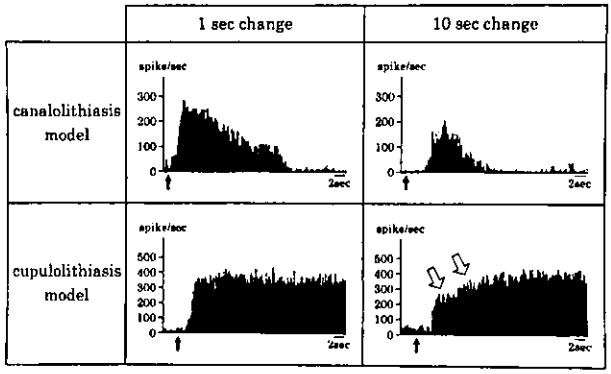

Fig. 4. Examples of the spike density histograms for the canalolithiasis and cupulolithiasis models in response to 1- and 10-s positional changes. Filled arrows indicate the onset of the positional change. Open arrows indicate the accumulation of the spikes after the positional change in the cupulolithiasis model.

were 382.6±23.3/s for the quick and 394.4±18.5/s for the slow change (p = NS). The discharges were sustained for a long time when the PSC was kept in the C-D position for both the quick and slow changes. The measured duration for both the quick and slow changes ranged from 40 to 130 min, with an average of ≈90 min. The mean latencies to the onset were 1.2±0.3 s for the quick and 2.6±0.8 s for the slow change and this difference was significant ($p < 0.05$). The mean latencies to the peak were 1.6±0.2 s for the quick and 7.5±1.6 s for the slow change and this difference was significant ($p < 0.05$). In the cupulolithiasis model, the quick change resulted in shorter latencies to the onset and the peak, but the maximum spike counts and the response duration did not differ significantly between the quick and slow changes (Figs. 4 and 5). A progressive accumulation of spikes for the slow change resulted in a longer peak latency (open arrows in Fig. 4).

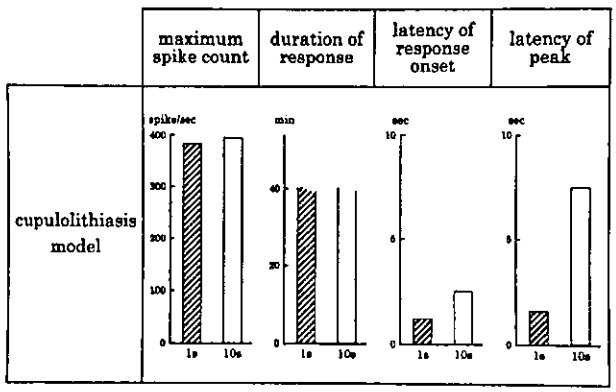

Fig. 5. The means of maximum spike count, duration of response, latency of response onset and latency of peak in the cupulolithiasis model. Hatched bars: values for 1-s positional change. Open bars: values for 10-s positional change.

DISCUSSION

BPPV is a common vestibular disorder characterized by rotational vertigo resulting from a change in head position. It usually takes a benign course and can be controlled by physical therapy. In some refractory cases, however, vertigo persists for several years. Various mechanisms of the etiology of BPPV have been proposed. Whilst the mechanism of cupulolithiasis suggested by Schuknecht (3) is widely known, Epley (4) and Brandt and Steddin (5) reported canalolithiasis to be a more likely mechanism. However, whether or not these two mechanisms can stimulate the sensory cells of the SC has not been evaluated. Suzuki et al. (8, 9), using a frog SC model, showed that both conditions effectively stimulate the sensory cells. Furthermore, based on the ampullary nerve discharge pattern (long latency and short duration), canalolithiasis is the most valid mechanism of BPPV. Clinicians are aware that patients with BPPV experience stronger vertigo upon quick motion. As a result, such patients take care to avoid making quick head movements. The velocity of the change of head position is perhaps a critical factor determining the occurrence and severity of vertigo. In this study, the etiological mechanism of BPPV was examined by physiologically analyzing the PSC nerve discharges obtained with slow and quick positional changes of the PSC.

In the canalolithiasis model, it was observed using a dissection microscope that the otoconia were accelerated and moved in a single mass upon the quick positional change. The otoconia gradually became lumped together and moved slowly upon the slow positional change. In any case, the basic motion pattern involved sliding along the canal wall. There was a latency before the otoconia began to move for both the quick and slow changes, and this latency depended on the velocity of the positional change. The maximum number of spike counts was greater, the response duration longer and the latencies to the response onset and the peak shorter when the positional change was quick. The spike density histogram showed a marked excitatory discharge with a short latency for the quick change, but a smaller, shorter response with a longer latency for the slow change. The otoconia moved with a greater acceleration for the quick change, evoking a more sustained and greater discharge with a shorter latency.

In the cupulolithiasis model, the maximum number of spike counts and the response duration did not differ significantly between the quick and slow

changes. The discharges were sustained as long as the PSC was maintained in the C-D position. The latencies to the response onset and the peak were shorter for the quick change. For the slow change, the discharges accumulated slowly, resulting in a relatively long peak latency. This progressive accumulation of the spikes was possibly due to an increasing gravity vector located along the plane of the cupula surface.

An important factor affecting the conduction velocity of a myelinated nerve is the diameter of the nerve fiber. Neurons with a small diameter have a slow conduction velocity and a high threshold for rotational acceleration (10, 11). They fire regularly in a tonic fashion. In contrast, neurons with a large diameter have a fast conduction velocity and a low threshold for rotational acceleration and fire irregularly in a phasic fashion. According to morphological studies of vestibular hair cells, mammals and birds (12) have two types, type I and type II, whilst frogs and other lower vertebrates have only type II cells. The largest nerve fibers (6–9 μm) are distributed primarily in type I cells, with small fibers (1–2 μm) in the type II cells. Frogs have only type II cells, but their nerve fibers show different physiological properties (11). PSC nerves of various sizes possibly respond to different accelerations upon quick and slow positional changes. The acceleration of the otoconia in the PSC was greater for the quick change, where both phasic and tonic units contributed to a greater discharge with a longer duration. For the slow positional change, phasic units with a lower threshold mainly responded, resulting in a smaller discharge with a shorter duration. In the cupulolithiasis model, the tonic units primarily responded to the sustained gravitational force acting on the cupula.

The results of our experiments demonstrate that the canalolithiasis model influences the discharge magnitude of the PSC according to the speed of the positional change. This suggests that canalolithiasis is the more likely mechanism of BPPV, which is characterized by various degrees of vertigo upon kinetic positional change. There is a less common type of positional vertigo characterized by sustained nystagmus evoked by a static head position; cupulolithiasis is potentially a mechanism of this type of positional nystagmus.

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眼振の推移からみた半規管遮断術の効果

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The Effect of Canal Plugging Evaluated by Positional Nystagmus

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Clinical effect of a canal plugging procedure was evaluated by positional nystagmus findings. A 61-year-old woman had complained of positional vertigo for the past 8 years. Vertigo was exacerbated when her head position was with the right side down. The positional nystagmus varied at every examination. They were direction-changing geotropic, or apogeotropic nystagmus, direction-changing rotatory nystagmus etc. Other neurootological tests were negative. From the findings of nystagmus, combined lesions involving the utricle, horizontal and posterior semicircular canals were suspected. Since her response to physical therapy was minimum, canal plugging surgery to the right horizontal canal was indicated. After surgery, all types of nystagmus as well as vertigo disappeared, suggesting an inhibitory effect of canal plugging on the whole vestibular organ.

Key words : positional vertigo, canal plugging, horizontal semicircular canal

はじめに

良性発作性頭位めまい症（BPPV と略す）は頻度の高いめまい疾患で，その特徴ある臨床像と理学療法の効果が高いことから近年注目を集めている[1)2)]．短時間のめまいや眼振所見から後半規管の半規管結石症が病因である可能性が高い．一方，BPPV と類似した症状を有するが，主として側臥位で眼振が出現し，方向交代性下向性頭位眼振を示す症例がある．これは側臥位型あるいは外側半規管型 BPPV と呼ばれることがあり，病態として外側半規管の半規管結石症が考えられる．今回，外側半規管の半規管結石症と考えられた頭位性めまい症例に半規管遮断術を行い，眼振の推移から半規管遮断術の効果について考察を加えたので報告する．

症例の提示

症例：61 歳，女性，主婦．

主訴：頭位変換時のめまい．

現病歴：平成 5 年 3 月頃より，主として右下頭位での

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めまいが出現した．以後，ほぼ1ヵ月ごとに3日から1週間ほど続く頭位性めまいを繰り返した．めまいは特に右下頭位で強く，また春季と秋季に増悪する傾向があった．蝸牛症状，神経症状の随伴はなかった．平成5年4月8日当科を初診した．

既往歴：特記すべきことなし．

当科初診時の検査所見：耳鼻咽喉科的局所所見に異常はなかった．聴力は正常範囲であった．また，脳神経症状や小脳症状もみられなかった．注視眼振はなかったが，頭位眼振検査にて左下頭位にて左向きの水平回旋混合性眼振を認めた．症状は比較的軽く，保存的療法によく反応したので末梢性の頭位性めまいとして以後対症的に重曹水注射，抗めまい薬の投与を行っていた．平成9年10月21日からさらに詳しい神経耳科的検査を施行した．

平成9年以後の神経耳科学的検査所見：オージオグラムは右左ともに平均10.0 dBで，注視眼振はなかった．重心動揺検査は正常範囲で，温度刺激検査も異常なく，前庭誘発筋電位も両側良好な反応が得られた．OKP，ETTともに正常であった．

頭位・頭位変換眼振検査では特徴的な眼振所見が得られ，経時的に変化したので，以下に順を追って主な所見を示す．平成9年10月21日の検査では，方向交代性下向性水平回旋混合性頭位眼振がみられた．以後眼振は頭位変換時よりも静止頭位時に著明で，方向交代性回旋性頭位眼振，方向交代性上向性頭位眼振，さらに方向交代性垂直回旋混合性頭位眼振などへと変化した（図1）．めまいは特に右下頭位で強く，眼振の強さに比例していた．

平成9年以後の経過：静止時の頭位で方向交代性下向性頭位眼振や方向交代性上向性頭位眼振がみられたことから，右外側半規管の半規管結石症やクプラ結石症が病態の一つと考えられた．さらに頭位性の回旋性眼振もあり，この眼振は微弱でめまい感もほとんどないことから耳石系の障害も疑われた．また，垂直回旋混合性眼振からは後半規管由来の病巣も考えられ，右側の複数の前庭器官を含む病巣が疑われた．外側半規管や後半規管の病巣を想定して頭位変換療法を行ったが，めまいは一時的に軽快したのみで永続的な効果は得られなかった．

平成12年12月頃よりめまいが頻発するようになり，特に平成13年6月には強度の方向交代性下向性頭位眼振が出現した（図2）．本人も根治的な治療を希望したので半規管遮断術にふみきった．遮断する半規管としては，方向交代性下向性頭位眼振が最も強い症状を起こし，また頻繁に出現していたので右外側半規管を選択した．

手術所見：平成13年6月21日，全身麻酔下に手術を

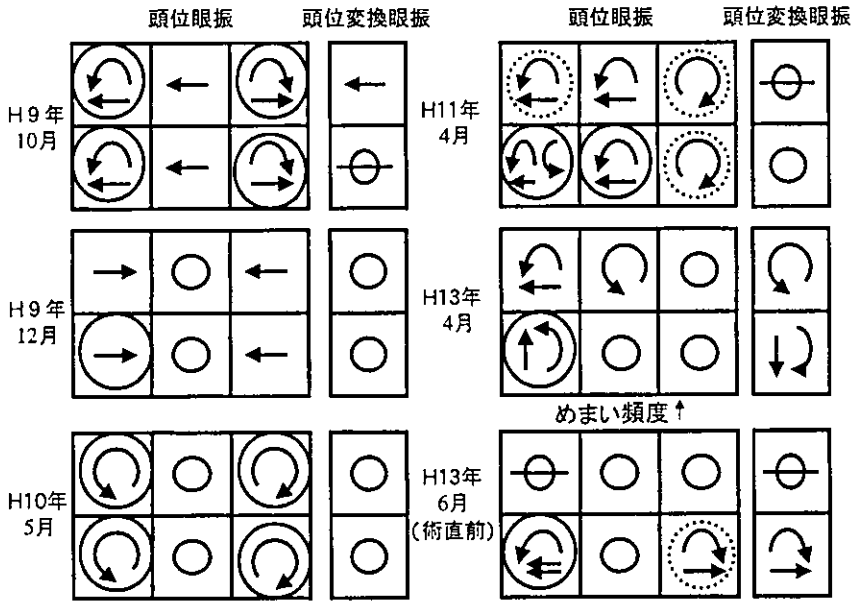

図1　頭位眼振，頭位変換眼振の経過
検査時期により，方向交代性下向性眼振，方向交代性上向性眼振，方向交代性回旋性眼振などへと変化した．

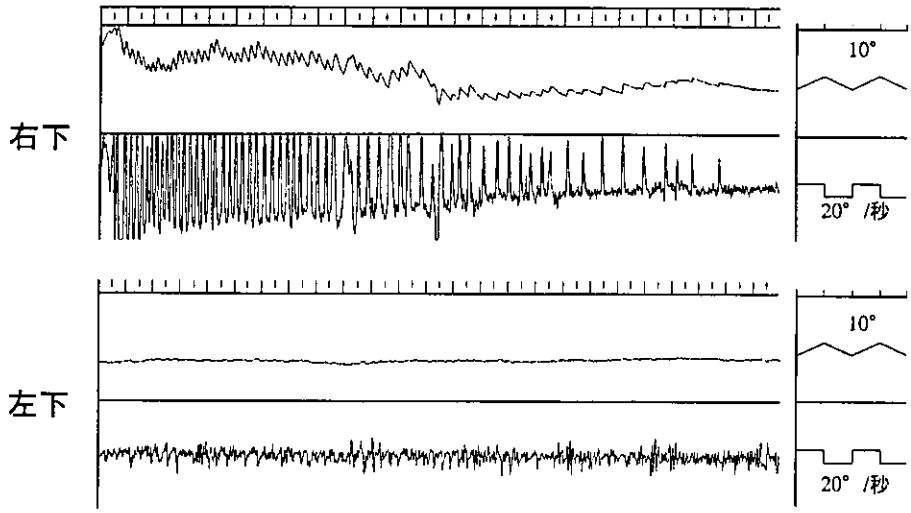

図2　半規管遮断術直前の頭位眼振のENG所見
右下頭位で著明な右向き眼振がみられる．

施行した．通常の耳後切開に続いて乳突削開を行った．乳突洞を開放して外側半規管隆起を削開し，ブルーラインを確認した．ブルーラインに相当する箇所に楕円形に細い溝を作製し，この溝を手がかりとして骨片を除去し，半規管を開窓した．開窓部に骨パテの球状の小片を2個挿入し，骨片とフィブリン糊で閉鎖し，筋膜で半規管削開部全体を覆い手術を終了した．

術後経過：術後翌日から4日目までは仰臥位正中位と左右下頭位で右向き水平回旋混合性眼振がみられた．以後は右下頭位での微弱な純回旋性眼振のみとなった（図3）．3日目に独歩を開始し，4日目より通常の歩行が可能となったが，急激な頭の回転時と右下頭位では軽いめまいがあった．めまい感は次第に軽快していき，7月2日，術後11日目に退院した．7月31日の外来受診時にはすべての頭位眼振は消失しており，右下頭位でもめまいは全く感じなくなった．また，術前までは右下頭位を避ける習慣があったが，いかなる頭位も可能となり，患者の満足度はきわめて高いものであった．平成14年2月現在，めまいとすべての眼振は完全に消失している．

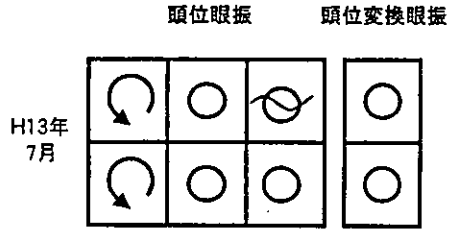

図3　平成13年7月10日（術後19日目）の眼振所見
右下頭位で微弱な眼振がみられるのみとなった．

聴力は術後11日目に平均53.3 dBの混合性難聴をきたしたが，その8日後には正常レベルまで回復した．術後の温度眼振反応は消失した．

考　察

末梢性の頭位性めまいは一般に予後良好で，いわゆるBPPVは近年の病態を想定した理学療法などで特に早期の治癒が期待できるようになった[3)～6)]．一方，まれではあるが，薬物療法や理学療法に抵抗し，めまい症状と恐怖感が強く頭位眼振検査さえも不可能な症例がある．これに対しては半規管遮断術が適応になる．

遮断術の長所としては，特別の器具や技術を要しない，遮断効果は単一の半規管に限局される，聴力が保存できる，早期離床が可能である，再発がない，などが挙げられる．短所としては，一過性に聴力が低下することが多い，まれではあるが永続的な感音難聴の可能性がある，入院が必要なことであろう．われわれは以下の条件を適応としている．(1) 頭位性めまいを頻繁に起こし，めまいの程度が強く，日常生活に支障をきたす．(2) 頭位変換療法を含む他の治療に抵抗する．(3) 病巣となる半規管が同定できる．(4) 中耳に炎症所見がない．(5) 唯一

聴耳でない．また，術前の説明と同意に関しては，以下の点を特に詳しく説明している．(1) 術直後は数日めまい感が増強する可能性がある．(2) 頭位変換時のめまいは消失しても浮遊感や不安定感が残存する可能性がある．(3) 感音難聴発生の可能性がある．

耳鼻咽喉科医がまず懸念するのは感音難聴の発生であろう．遮断術後は一過性の感音難聴が起こるとする報告が多い[7][8]．自験例でも40 dB程度の一過性の感音難聴が生じた．したがって術後の予防的ステロイド投与は必要と思われる．人の膜迷路はきわめて薄いので注意深く遮断を行っても多少の膜迷路障害，ひいては内耳障害の発生する可能性はある．膜迷路障害による漿液性内耳炎，あるいは内外リンパの電解質異常などが生じるものと推測される．実際，症例によっては術後麻痺性眼振のみられることがあり，これは内耳機能低下を示唆するものであろう．

鈴木[9]のサルを使った実験によると，半規管遮断術後も感覚上皮の形態は保たれ，感覚細胞の機能は維持されるという．すでに報告[10]したように，後半規管遮断術後は温度眼振反応が維持されること，聴力が保たれること，さらに数日で刺激性眼振が消失し，早期離床と歩行が可能になったことから手術の主たる影響は遮断した半規管に限局するとしてよいであろう．今回の症例も外側半規管由来と考えられる眼振とめまい症状は術直後から消失し，遮断術の効果と考えられた．卵形嚢や後半規管由来の回旋成分の強い眼振は術後も残存すると予想したが，それに反してこれらも全く消失した．いかなる頭位でも眼振は出現しなくなったことから右前庭系全体の機能低下が起こったことが推測された．ただし，めまい症状や眼振の消失はすみやかであったこと，すでに報告したように後半規管遮断術後の温度眼振反応は保たれることなどから，前庭機能が高度に低下したとは考えにくい．頭位の変化で誘発されない程度に卵形嚢や後半規管の反応閾値を上昇させる効果となったものと考えられる．

すでに本法の効果は欧米では多く報告されており，われわれ[8][11]も自験例ならびに両生類の半規管を用いたモデル実験で半規管遮断術の効果の高いことを確認した．今回，半規管遮断術は目的とする半規管機能を選択的に遮断できるほか，他の前庭器の機能もある程度抑制する効果があると考えられたので，今後症例を蓄積することにより頭位性めまいに対する適応を明らかにしていきたい．

まとめ

多彩な眼振所見を示した頭位性めまい症例に対し，外側半規管遮断術を施行した．術後すべての眼振が消失し，遮断の効果は遮断半規管のみならず他の前庭器にも及ぶものと推察した．

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Radical Scavengers for Ménière's Disease after Failure of Conventional Therapy: A Pilot Study

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Objective—To perform a trial to assess the efficacy of radical scavengers, i.e. rebamipide, vitamin C and glutathione, for the treatment of Ménière's disease (MD).
Material and Methods—Rebamipide (300 mg/day), vitamin C (600 mg/day) and/or glutathione (300 mg/day) were given orally for at least 8 weeks to 25 patients with poorly controlled MD.
Results—Of 22 patients, 21 showed marked improvement of vertigo; 12/27 ears showed improvement of hearing disorders; 17/27 ears showed improvement of tinnitus; and 18/25 patients showed improvement of disability.
Conclusion—This study suggests that treatment using radical scavengers has the potential to become an effective new therapy for MD. *Key words: Ménière's disease, pilot study, radical scavengers.*

INTRODUCTION

Ménière's disease (MD) is a syndrome of peripheral cochleo-vestibular origin in which vertigo coincides with (initially fluctuating) hearing loss, tinnitus and aural fullness. All three symptoms, either separately or in combination, cause great distress and have a considerable impact on the patient's quality of life (1). A number of pharmacological treatments have been applied in MD, e.g. antihistamines, neuroleptic drugs and diazepam for treatment of the attacks of acute vertigo and vasoactive drugs, betahistine and diuretics for long-term management. In particular, diuretics such as acetazolamide, isosorbide and thiazide diuretics are widely used to reduce the endolymphatic hydrops (2, 3). It has been reported that episodes of vertigo generally abate after 10–20 years of MD (4). Silverstein et al. (5) reported a spontaneous resolution of vertigo in 51% and 71% of MD patients after 2 and 3 years of symptomatic therapy, respectively. However, some patients experience poor control of vertigo even after several years of treatment and the cochlear hearing loss generally progresses. The rate of hearing loss in MD is $\approx$ 1.5–2.0 dB/year and hearing loss eventually plateaus at 50–60 dB (4, 6). Treatment for MD mainly aims to reduce one of the symptoms, the attacks of vertigo, because no treatment (with the exception of hearing aids) has demonstrated any positive long-term effect on hearing loss or tinnitus (1). Some review articles on the medical treatment of MD concluded that although many medical therapies purport to be successful in terms of treatment of vertigo none seem to have any benefit on hearing (1–3).

Recently, evidence has accumulated to suggest that free radicals may play an important role in inner ear disorders; free radical scavengers can be used not only to prevent but also to treat inner ear disorders (7, 8). Concerning MD, Horner and Guilhaume (9) suggested that oxidative insult is likely to contribute to the pathology associated with endolymphatic hydrops and thus that free radical scavengers might be useful in the treatment of MD patients. In addition, Shinomori and Kimura (10) reported that allopurinol, a xanthine oxidase inhibitor and free radical scavenger, may attenuate endolymphatic hydrops and cell damage by preventing the formation of free radicals or by scavenging free radicals. These findings may lead to a new treatment for MD. Based on these results, we carried out this pilot study to determine whether radical scavengers can be used to treat patients who fall into the "poor prognosis" category, i.e. those who do not respond to conventional medical treatment.

MATERIAL AND METHODS

The study subjects were recruited from a group of registered MD patients at the Departments of Otolaryngology of Hiroshima University Hospital and Omichi Hospital, Osaka. Based on history and audiometric data, each patient was classified as having definite MD in accordance with the 1995 guidelines of the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology—Head and Neck Surgery (CHE AAO-HNS) (11). Patients participating in the study met the following criteria: poor control of vertigo and/or progressive or continuing hearing loss after $\geq$ 2 months of conventional treatment. A detailed explanation of the study, including risks and possible benefits, was provided to all patients and their informed consent was obtained. The average age of the 25 patients (9 males, 16 females) was 49.8 years (range 27–65 years). In 12 patients the right ear

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was affected, in 11 the left ear was affected and in 2 both ears were affected. Patients received rebamipide 300 mg/day, vitamin C 600 mg/day and/or glutathione 300 mg for at least 8 weeks. Drugs were weaned after 6 months with no major spells of vertigo or when patients wanted to discontinue treatment.

Effects on hearing, vestibular function, tinnitus and general condition, as well as possible side-effects, were investigated. Evaluation of symptoms was made in accordance with the guidelines for reporting treatment results in MD of the Committee of the Japan Society for Equilibrium Research (CJpER) (12), which are almost the same as the CHE AAO-HNS guidelines.

Evaluation of vertigo

Only definite vertiginous spells with spontaneous nystagmus were considered for evaluation. The formula expressing the effect of treatment on vertigo is as follows: the average number of definitive vertiginous spells per month for 4 weeks, 8 weeks and 12 months after the start of treatment divided by the average number of definitive vertiginous spells per month for 6 months before treatment was begun. If the duration of pre-treatment observation was < 6 months, the divisor was the average number of definitive vertiginous spells per month over the period of observation. When multiplied by 100 this fraction gave a figure representing the effect of treatment on the vertiginous spells. Six categories were defined: 0 = complete control of definitive vertiginous spells; 1–40 = substantial control of definitive vertiginous spells; 41–80 = limited control of definitive vertiginous spells; 81–120 = insignificant control of definitive vertiginous spells; > 120 = poorer control of definitive vertiginous spells; and secondary treatment initiated due to disability resulting from vertigo (11, 12).

Evaluation of hearing

The determination of hearing change was based on the four-frequency pure-tone average (PTA) of thresholds at 250, 500, 1000 and 2000 Hz. This determination was made by comparison of the pre-treatment hearing level and that after 4 weeks, 8 weeks or 12 months of treatment. A change of ≥ 10 dB was considered clinically significant (12). In addition to this guideline (CJpER), hearing was also evaluated by comparison of the individual pure-tone thresholds at 125, 250, 500, 1000, 2000, 4000 and 8000 Hz. Hearing change was determined by comparison of the pre- and post-treatment hearing levels. The pre-treatment hearing level was determined as the poorest hearing level obtained in the 6 months before treatment. The post-treatment hearing level was determined by the poorest hearing level measure obtained 10–14 months after the start of therapy.

Evaluation of tinnitus

Tinnitus was classified into one of five grades by consideration of subjective symptoms (CjpER guidelines) as follows:

1. Slight = only heard in a quiet environment, very easily masked. No interference with sleep or daily activities.
2. Mild = easily masked by environmental sounds and easily forgotten during activity.
3. Moderate = may be noticed even in the presence of background or environmental noise although daily activities can still be performed. Less noticeable when concentrating. Not infrequently interferes with sleep and quiet activities.
4. Severe = almost always heard, rarely if ever masked. Leads to disturbed sleep pattern and can interfere with ability to carry out normal daily activities. Quiet activities adversely affected.
5. Catastrophic = all tinnitus symptoms at the level of severe or worse.

The treatment outcome regarding tinnitus was expressed as improved, unchanged or worse for each patient by comparing the pre- and post-treatment scores.

Evaluation of disability

Functional impairment and disability was evaluated by means of a six-point functional level scale introduced by the CHE AAO-HNS (11). The treatment outcome regarding disability was expressed as improved, unchanged or worse for each patient by comparing the pre- and post-treatment scores.

RESULTS

The average duration of disease was 44 months (range 7–180 months). Hearing impairment before therapy was seen in all patients, and poor control of vertigo was seen in 22 patients. Staging of MD was made according to the CHE AAO-HNS guidelines as follows: stage 1, $n = 9$; stage 2, $n = 7$; stage 3, $n = 6$; stage 4, $n = 3$. The average duration of radical scavenger therapy was 7.6 months (range 2–14 months). Three typical cases are reported in Fig. 1.

Case 1

A 66-year-old man complained of recurrent episodic vertigo and left hearing impairment. The duration of disease was 20 months. He was treated with diuretics, betahistine, vasoactive drugs, etc. but without relief. After radical scavenger therapy he achieved complete control of vertigo (number of episodes of vertigo/month $4 \rightarrow 0$) and his hearing improved. Tinnitus

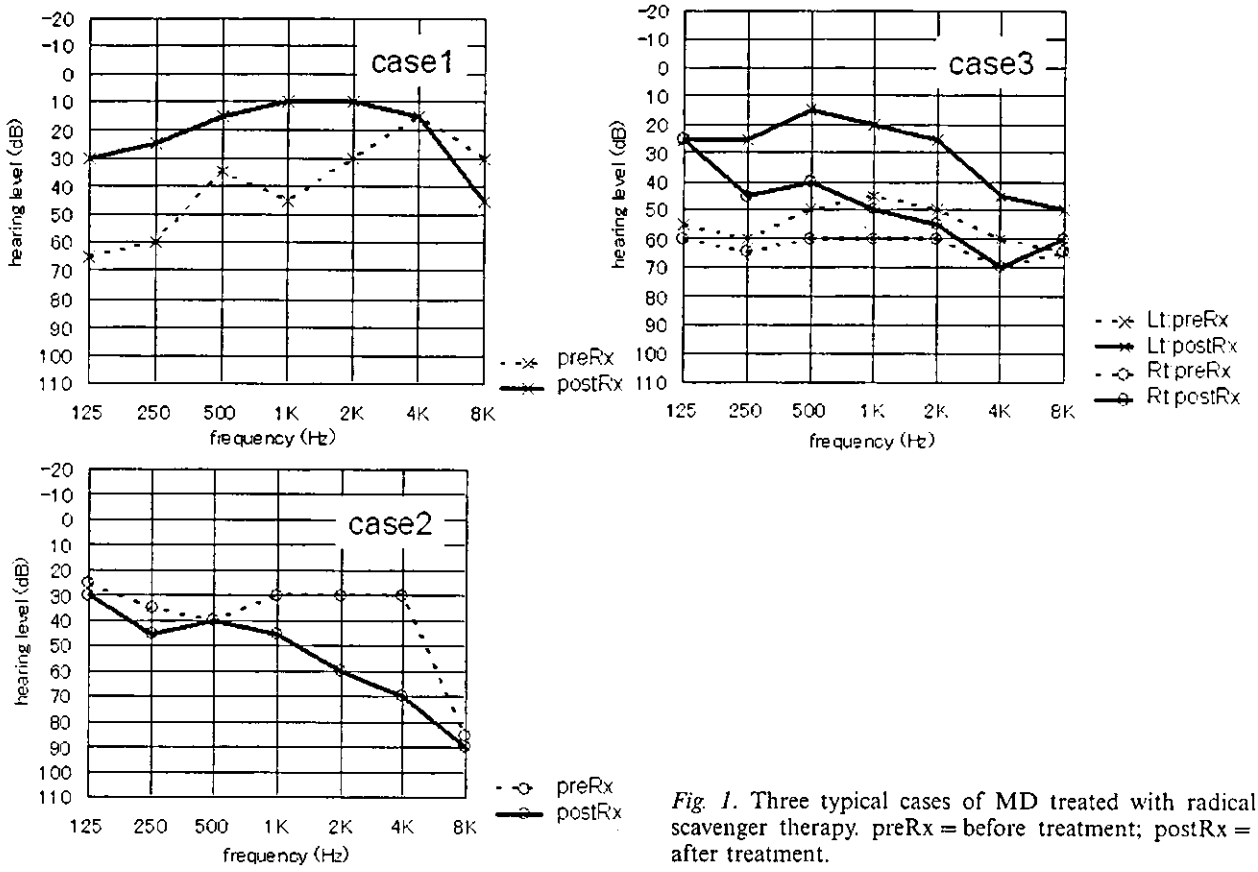

Fig. 1. Three typical cases of MD treated with radical scavenger therapy. preRx = before treatment; postRx = after treatment.

grade improved (4→1). Disability improved (functional level scale 3→1).

Case 2

A 50-year-old man complained of recurrent episodic vertigo and right hearing impairment. The duration of disease was 8 months. He was treated with diuretics, betahistine, vasoactive drugs, steroids, water restriction, etc. but without relief. After radical scavenger therapy he achieved complete control of vertigo (number of vertigo episodes/month 6→0) whilst hearing loss progressed in the high frequencies. Tinnitus grade improved (2→1). Disability improved (functional level scale 3→1).

Case 3

A 47-year-old man complained of bilateral hearing impairment. The duration of disease was 144 months in the right ear and 84 months in the left. He was treated with diuretics, betahistine, vasoactive drugs, steroids, etc. but without relief. After radical scavenger therapy hearing was markedly improved in the left ear but only in the low frequencies in the right ear. Tinnitus grade improved (3→1 for the right ear, 2→1 for the left). Disability improved (functional level scale 2→1).

Evaluation of vertigo

Three patients who had only hearing impairment were excluded for the evaluation of vertigo. The average CHE AAO-HNS vertigo severity was 8.4%; in other words, after 12 months of follow-up, patients experienced an average of 8.4% of the number of vertigo episodes they had experienced before treatment. Twelve months after beginning treatment, 16 (72.7%) patients had complete control of vertigo, 5 (22.7%) had substantial control, 1 (4.6%) had insignificant control and no patient had limited or worse control. Regarding short-term follow-up, 10 (45.4%) patients had complete control, 11 (50.0%) had substantial control and 1 (4.6%) had insignificant control after 4 weeks and 14 (63.6%) had complete control, 7 (31.8%) had substantial control and 1 (4.6%) had worse control after 8 weeks. Pre-treatment vertigo frequency data (number of episodes/month) were compared with the data at an average of 4 weeks, 8 weeks and 12 months post-treatment (Fig. 2). The frequency of episodes of vertigo decreased significantly between pre-treatment and 4 weeks, 8 weeks and 12 months post-treatment ($p < 0.01$; ANOVA), as well as between 4 weeks and 12 months post-treatment ($p < 0.05$). No statistically significant decrease in the frequency of

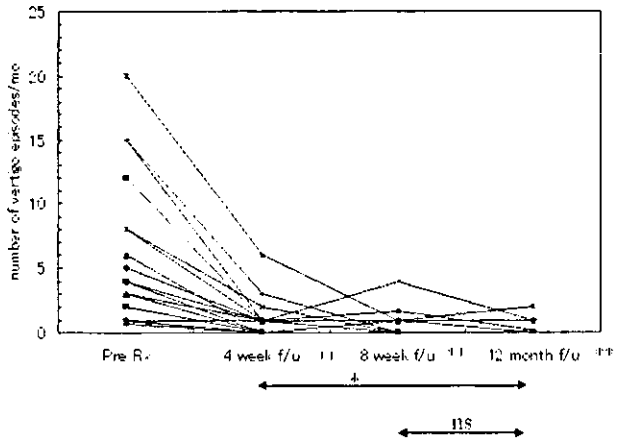

Fig. 2. The average number of episodes of vertigo per month for individual patients plotted at 4 points in time: before medical therapy and 4 weeks, 8 weeks and 12 months after. $*p < 0.05$; $**$ $p < 0.01$; ns = not significant; Pre Rx = before treatment.

episodes of vertigo occurred between 4 and 8 weeks or between 8 weeks and 12 months post-treatment.

Evaluation of hearing

The treatment outcome regarding hearing was evaluated in 27 ears. The average pre-treatment PTA threshold was 41.3 dB, which differed significantly ($p < 0.01$) from the PTA threshold after 12 months follow-up of 31.6 dB. On the basis of the CJpER guidelines for hearing, after 12 months follow-up 12 (44.4%) patients had improved, 14 (51.9%) were unchanged and 1 (3.7%) was worse. The improvement rate was 37% after both 4 and 8 weeks (Fig. 3). In addition, hearing was also evaluated by comparison of the individual pure-tone thresholds at 125, 250, 500, 1000, 2000, 4000 and 8000 Hz. The thresholds after 12 months follow-up were improved compared to pre-treatment thresholds at 125, 250, 500, 1000 ($p < 0.01$) and 2000 Hz ($p < 0.05$) but unchanged at 4000 and 8000 Hz (Fig. 4). The individual pure-tone threshold was also compared before treatment and after 12 months of follow-up. Some patients with moderate or severe hearing loss revealed a degree of recovery of hearing (Fig. 5). The pre- and post-treatment PTAs for each patient were compared between groups with different stages of MD to determine whether or not the stage of MD influenced the outcome. PTA gain did not differ between the groups (Fig. 6).

Evaluation of tinnitus and disability

The treatment outcome regarding tinnitus was evaluated in 27 ears. The grade of tinnitus decreased significantly ($p < 0.01$) between the pre-treatment period and 4 weeks, 8 weeks and 12 months post-treatment. No statistically significant decrease in tinnitus grade occurred between 4 weeks, 8 weeks and 12 months post-treatment (Fig. 7). On the basis of the guidelines for tinnitus, 17 (63%) patients were improved after 12 months follow-up, 16 (63%) after 4 weeks and 17 (59%) after 8 weeks (Fig. 3).

The treatment outcome regarding disability was evaluated in 25 patients. The functional level scale (disability) decreased significantly ($p < 0.01$) between the pre-treatment period and 4 weeks, 8 weeks and 12 months post-treatment, as well as between 4 weeks and 12 months post-treatment ($p < 0.05$). No statistically significant decrease in tinnitus grade occurred between 8 weeks and 12 months post-treatment. Disability was improved in 18 (72%) patients after 12 months of follow-up, 14 (56%) after 4 weeks and 17 (68%) after 8 weeks (Fig. 3).

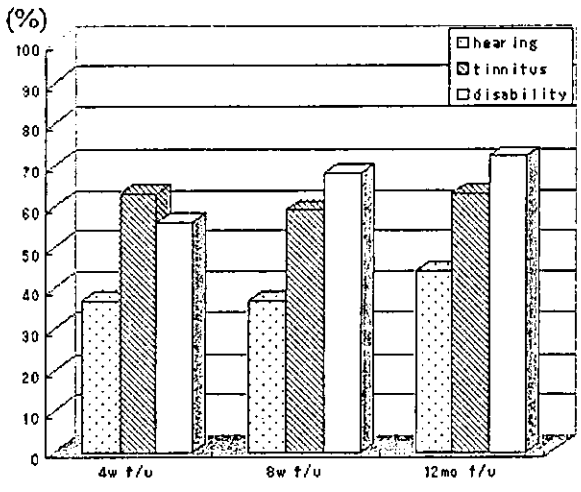

Fig. 3. Improvements in hearing, tinnitus and disability after 4 weeks, 8 weeks and 12 months of treatment.

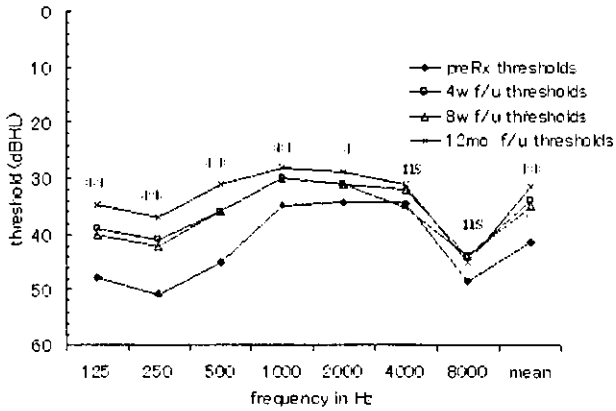

Fig. 4. Audiogram showing average thresholds at each octave for patients before treatment (preRx) and at an average of 4 weeks, 8 weeks and 12 months post-treatment. $*p < 0.05$; $**p < 0.01$; ns = not significant.

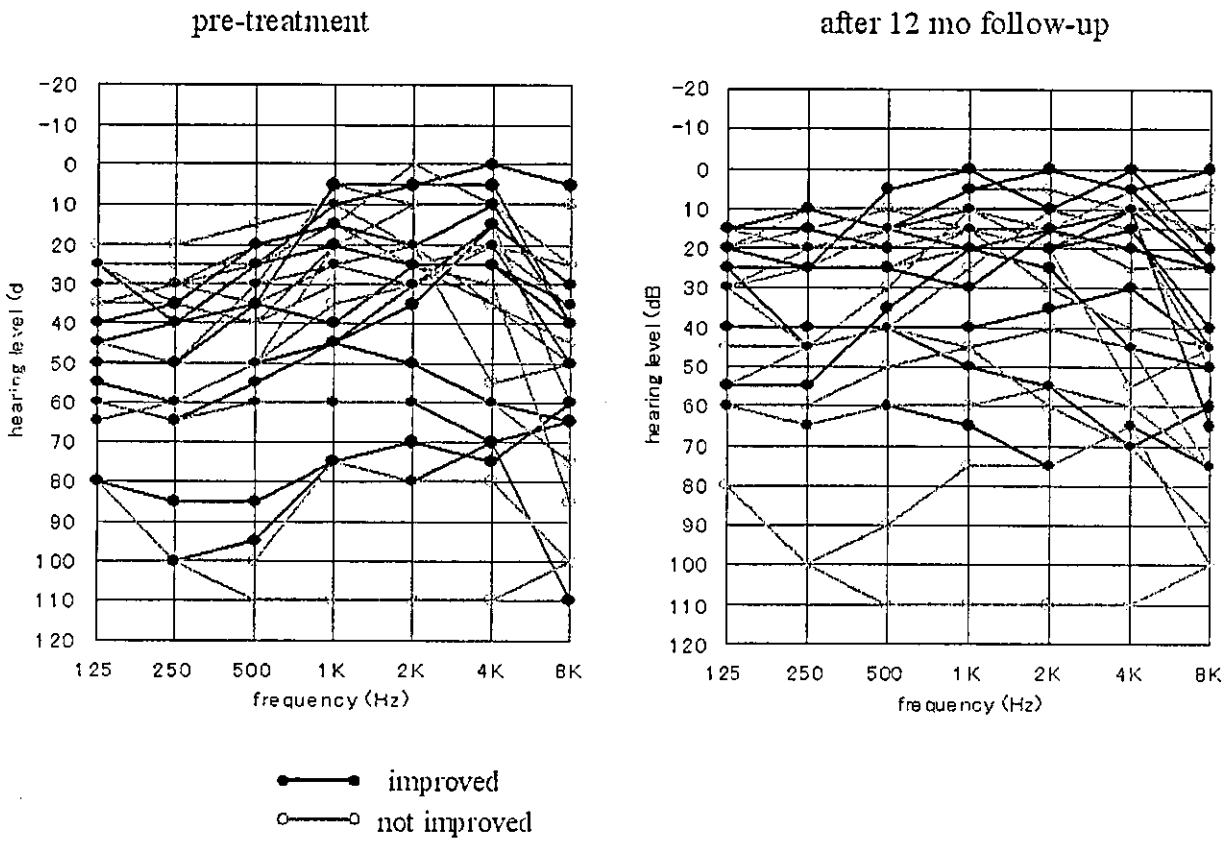

Fig. 5. Comparison of individual audiograms before treatment and 12 months post-treatment. Improved cases are plotted using dark lines.

DISCUSSION

The natural course of MD was described by Friberg et al. (6) in a retrospective study of 161 MD patients followed up for ≥ 9 years. They showed that, after 5–10 years of disease, the cochlear hearing loss stops at a hearing level of 50–60 dB and the vestibular loss at a caloric response $\approx 50\%$ of normal, and that the frequency of vertigo attacks decreases after ≈ 2 decades. Concerning the medical treatment of MD, Torok (13), in 1977, concluded that all medical treatments have one common feature, namely that they were all purported to be successful, but not in 100% of cases, recovery varying from 60–80%. Arenberg and Bayer (14) concluded that, although many medical therapies were purported to be successful in terms of vertigo, none seem to have any benefit on hearing. Based on these results, stabilization or improvement of hearing is one of the main purposes of the treatment of MD.

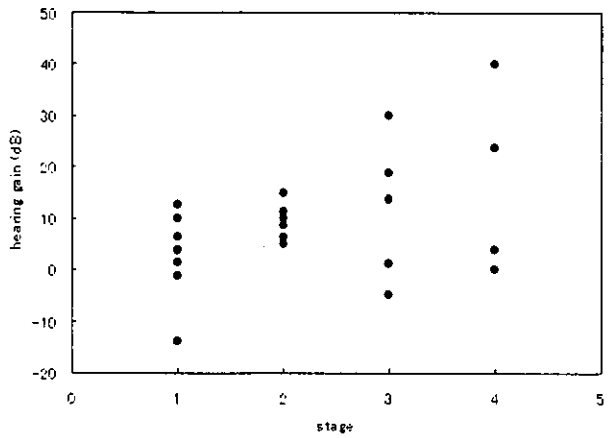

Fig. 6. PTA gains for individual patients with different stages of MD.

Recently, it has been demonstrated that free radicals, i.e. nitric oxide and reactive oxygen species (ROS), may play an essential role in certain inner ear disorders, such as acoustic trauma, labyrinthitis, aminoglycoside ototoxicity, cisplatin ototoxicity and MD (7). It has also been demonstrated that inner ear damage caused by aminoglycosides is ameliorated by the presence of radical scavengers and glutathione synthesis inhibitors. ROS scavengers have been shown to provide protection from inner ear damage caused by aminoglycoside, cisplatin, lipopolysaccharide-induced labyrinthitis and acoustic trauma (7, 8, 15). Based on these basic findings, we hypothesized that free radical formation in the inner ear may play an

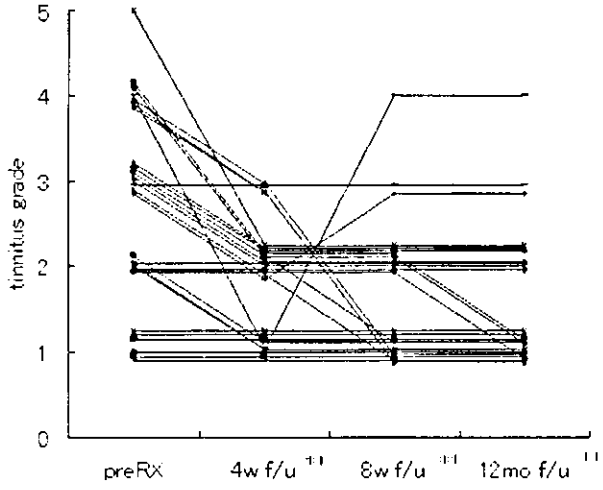

Fig. 7. Tinnitus grades for individual patients plotted at 4 points in time: before medical therapy and 4 weeks, 8 weeks and 12 months after. $^{**}p < 0.01$.

important role in the pathogenesis of MD and that radical scavengers may be useful for the treatment of MD (7, 9, 10).

In order to apply radical scavengers for the treatment of MD, we selected rebamipide, vitamin C and glutathione as these drugs act as radical scavengers and have already been widely used for other purposes, i.e. for the treatment of gastric ulcers, liver dysfunction and vitamin deficiency. In addition, we have already applied these drugs for the treatment of cisplatin-induced hearing loss and obtained satisfactory results (16). That preliminary study demonstrated that radical scavenger therapy resulted in adequate control of vertigo and recovery of hearing after the failure of conventional medical treatment of MD. Concerning vertigo, $\approx 70\%$ patients achieved complete control. This is similar to the results obtained with other medical treatments (2, 3). However, it must be considered that all patients in the study did not obtain any relief after previous medical treatment. This suggests that patients treated with radical scavengers did not improve spontaneously but rather due to further treatment with radical scavengers.

Evaluation of hearing changes in patients with MD after radical scavenger therapy, based on the CJpER guidelines, revealed that 44.4% had improved hearing, 51.9% had no change and 3.7% had worse hearing. These values are consistent with or better than those reported in similar previous studies (2, 3, 17). In general, hearing loss is considered an unavoidable feature of the natural history of MD despite adequate medical or surgical therapy. Klockhoff et al. (17) demonstrated stabilization or improvement of the PTAs with diuretic therapy. Santos et al. (18) suggested that diuretics and a low-salt diet may decrease the natural progression of sensorineural hearing loss in patients with MD. Our results are preliminary and involved a short follow-up period. However, considering that all patients in this study had been using osmotic diuretics, mainly isosorbide, with no improvement in hearing, radical scavenger therapy has the potential to become an effective new therapy for MD.

An unexpected finding of the study was that some MD patients staged 3 or 4 (i.e. with severe hearing loss) also had the capacity to recover. In fact, hearing usually fluctuates early during MD, especially in the low frequencies, while patients with severe hearing loss are less likely to recover. This study demonstrated that some patients with the flat type of hearing loss (>40 dB) showed recovery of hearing. This fact may also suggest the efficacy of this therapy. We demonstrated significant threshold improvement at 125, 250, 500, 1000 and 2000 Hz, but no significant improvement at 4000 and 8000 Hz. These findings are consistent with those of similar previous studies (17, 18). However, some patients showed clear improvements at 4000 and 8000 Hz. In animal experiments, it has been suggested that inner ear sensory cells are capable of sustaining sub-lethal damage, while it is almost impossible to recover function after complete cell death. This is also in the case for human subjects. The fact that some patients showed recovery and others did not demonstrates the limitation of this therapy. In other words, all medical treatments may have the potential to improve symptoms but at the same time they all have limitations, in this case complete inner ear sensory cell death.

In conclusion, the present study revealed that treatment using radical scavengers has the potential to become an effective new therapy for MD. However, this was only a preliminary study with a short follow-up period. Further evaluation of this treatment modality for the control of vertigo and recovery of hearing after the failure of conventional treatment of MD is needed. In addition, a well-controlled randomized study should be performed in order to reveal the efficacy of this treatment.

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Neuroprotection of Vestibular Sensory Cells from Gentamicin Ototoxicity Obtained Using Nitric Oxide Synthase Inhibitors, Reactive Oxygen Species Scavengers, Brain-derived Neurotrophic Factors and Calpain Inhibitors

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Takumida M, Anniko M, Shimizu A, Watanabe H. *Neuroprotection of vestibular sensory cells from gentamicin ototoxicity obtained using nitric oxide synthase inhibitors, reactive oxygen species scavengers, brain-derived neurotrophic factors and calpain inhibitors.* Acta Otolaryngol 2003; 123: 8–13.

Objective—In order to devise a new treatment for inner ear disorders, the efficacy of a nitric oxide synthase inhibitor (L-N^G-nitroarginine methylester [L-NAME]), a radical scavenger (D-methionine), a neurotrophin (brain-derived neurotrophic factor [BDNF]) and a calpain inhibitor (leupeptin) for protection from hair cell damage was investigated.

Material and methods—The effects of these drugs on gentamicin-induced production of nitric oxide (NO) and reactive oxygen species (ROS) were studied by means of the fluorescence indicators 4,5-diaminofluorescein diacetate and dihydrotetramethylrosamine. The effect on gentamicin-induced vestibular hair cell damage was examined by using an in vitro LIVE/DEAD system.

Results—L-NAME inhibited the production of NO, D-methionine and BDNF restricted the production of ROS and leupeptin inhibited neither NO nor ROS. All the drugs used limited the vestibular hair cell damage caused by gentamicin. The combinations L-NAME + BDNF, L-NAME + leupeptin and D-methionine + BDNF had a significantly stronger preventive effect on hair cell damage.

Conclusion—It is suggested that combined treatment with a radical inhibitor and either a neurotrophin or calpain inhibitor may help to treat inner ear disorders more effectively. *Key words: apoptosis, brain-derived neurotrophic factor, free radical, gentamicin, nitric oxide, vestibular hair cell.*

INTRODUCTION

Evidence is accumulating to suggest that generation of both nitric oxide (NO) and reactive oxygen species (ROS) is an important contributory factor in inner ear damage. In one study, blocking of N-methyl-D-aspartate (NMDA) receptor function by NMDA antagonists was shown in vivo to afford protection from aminoglycoside-induced hair cell damage (1). Moreover, inner ear damage caused by aminoglycosides is ameliorated by the presence of ROS scavengers (2) and glutathione synthesis inhibitors (3). ROS scavengers have been shown to provide protection from inner ear damage caused by aminoglycosides (2), cisplatin (4) and acoustic trauma (5). The other important free radical, NO, is also an important contributor to inner ear damage. In pathological conditions such as lipopolysaccharide (LPS)-induced labyrinthitis (6–8), glutamate-induced excitotoxicity (8), aminoglycoside ototoxicity (9) and cisplatin ototoxicity (10), excess production of NO resulting in the formation of peroxynitrite can give rise to morphological and functional inner ear disorders (7–9). In fact, we found recently that inoculation with LPS or gentamicin (GM) induced expression of nitric oxide synthase (NOS) II, with consequent functional disorders in cochleae and vestibula, which could be blocked using the NOS inhibitor L-N^G-nitroarginine methylester (L-NAME) and ebselen, a scavenger of peroxynitrite (7–9).

Target-mediated neuronal survival within the peripheral auditory and vestibular receptors has been shown to involve members of the nerve growth factor (NGF) family of neurotrophins. Indeed, a number of studies have now demonstrated the beneficial effects of brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) on the survival of compromised auditory and vestibular neurons (5, 11–13). Sudden withdrawal of exogenous BDNF and NT-3 from spiral ganglion neuron cell cultures resulted in apoptosis of the auditory neurons. Apoptosis, i.e. programmed cell death, occurring under pathological as well as physiological conditions, is now regarded as the main cause of inner ear damage to hair cells affected by an aminoglycoside (14). It has also been suggested that apoptosis in hair cells may be stimulated by acoustic overstimulation (15), cisplatin ototoxicity (16), LPS-induced ototoxicity (17) and by aging (18). Apoptosis of the auditory sensory cells can be prevented by treatment with either caspase inhibitors (16, 19) or calpain inhibitors (19, 20), which are known protease inhibitors involved in the apoptotic process.

Based on these findings, a number of investigations have been carried out with the intention of devising means to prevent inner ear damage. A problem in these earlier studies was the difficulty of obtaining complete morphological and functional protection. In order to solve this problem, the combination of ROS

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