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Effects of corticosteroid, contrast medium and ATP on focal microcirculatory disorders of the cochlea

Mitsuyoshi Nagura [a,*], Satoshi Iwasaki [a], Rong Wu [a], Kunihiro Mizuta [a], Kazuo Umemura [b], Tomoyuki Hoshino [a]

[a] *Department of Otolaryngology, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu, 431-3192, Japan*
[b] *Department of Pharmacology, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu, 431-3192, Japan*

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Abstract

We evaluated the ability of various drugs to prevent the decrease in focal cochlear blood flow induced by photochemical reaction and investigated the mechanisms underlying this decrease. By means of a photochemical reaction, which produces reactive oxygen species, focal lesions measuring about 1 mm in diameter were induced in the lateral wall of the guinea pig cochlea. The protective effects of hydrocortisone, amidotrizoate and ATP on cochlear blood flow and cochlear vascular conductance changes were evaluated by using a non-contact laser flowmeter. Cochlear blood flow and cochlear vascular conductance were decreased to 65.1 ± 4.9% (mean ± S.E.M.) and 57.0 ± 3.7% (mean ± S.E.M.) of the initial level 30 min after the start of the photochemical reaction, respectively. Hydrocortisone significantly prevented the decline in the cochlear blood flow and cochlear vascular conductance and reduced the area of stria vascularis degeneration in a dose-dependent manner. Neither amidotrizoate nor ATP significantly prevented the decrease in cochlear blood flow or cochlear vascular conductance. Hydrocortisone was more effective than vasodilators or other agents which increase cochlear blood flow in preventing the photochemically induced decrease in cochlear blood flow. This might be due to the antioxidative effects of hydrocortisone.

Keywords: Cochlea; Hydrocortisone; Amidotrizoate; ATP; Microcirculation disorder; Reactive oxygen species

1. Introduction

Many investigators have reported decreased cochlear blood flow as the cause of various sensorineural hearing disorders (Prazma, 1981; Thorne and Nuttall, 1987), including sudden sensorineural hearing loss (Zajtchuk et al., 1979; Johnson et al., 1984). Although the etiology of sudden sensorineural hearing loss is still controversial, clinical treatments are often based on this assumption, and vasodilators or other agents such as ATP are often used in an attempt to increase cochlear blood flow (Brechtelsbauer et al., 1994; Kallinen et al., 1997). Other researchers have suggested viral infection (Veltri et al., 1981), intracochlear membrane rupture (Simmonds, 1979) and autoimmune processes (Haynes et al., 1980) as causes of sudden sensorineural hearing loss. Hoshino et al. (1980) reported that viral infection during treatment for autoimmune disease might cause sudden sensorineural hearing loss. Shiraishi et al. (1991) reported that it was important to improve the circulation, even in cases of sudden sensorineural hearing loss due to viral infections.

Experimental models for assessing the effects of various drugs on cochlear microcirculatory disorders have been reported in an attempt to clarify the etiology and to establish a treatment for sudden sensorineural hearing loss. Umemura et al. (1990a, 1993) produced an animal model in which the cochlear action potential was suppressed completely and examined the effects of drugs in this model. Such a model may be of use in examining diffuse and severe disorders of cochlear function. Slight or moderate sudden sensorineural hearing loss typically shows a high recovery rate, and the pattern of audiogram test results seems to have prognostic value (Mattox and Simmonds, 1977; Byl, 1984; Shiraishi et al., 1991). Threshold elevation at particular frequencies and subsequent restoration of hearing seem to be the result of localized, transient cochlear damage. Thus, further investigation of microcir-

* Corresponding author. Tel.: +81-53-435-2252; Fax: +81-53-435-2253

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culatory disorders of varying severity and at various sites along the cochlea would be helpful in providing information necessary for proper treatment.

A photochemical reaction between rose bengal and photo-illumination results in the production of reactive oxygen species, namely singlet oxygen and hydroxyl radicals (Lee and Rodgers, 1987; Umemura et al., 1990a). Reactive oxygen species have been shown to cause injury to endothelial cells and to induce thrombosis (Watson et al., 1985; Asai et al., 1993). In a previous experiment, we made use of this photochemical reaction to produce focal lesions (approximately 1 mm in diameter) in the second cochlear turn of guinea pigs, and described the course of events and the evolution of morphological changes, as determined by scanning electron microscopy, transmission electron microscopy and light microscopy (Iwasaki et al., 1997; Miyashita et al., 1998).

In the present study, we used the same photochemical reaction as a means to assess the effects of drugs on the focal decrease in cochlear blood flow. Hydrocortisone, ATP and amidotrizoate (diatrizoate), three different types of drugs often used in the treatment of sudden sensorineural hearing loss (Ushisako and Morimitsu, 1988; Brechtelsbauer et al., 1994; Kallinen et al., 1997), were administered intravenously and their effects on cochlear blood flow were evaluated by using a non-contact laser flowmeter. After cochlear blood flow was recorded, the area of stria vascularis degeneration was measured, using a scanning electron microscope, for quantification of cochlear damage.

2. Materials and methods

2.1. Animal preparation

Forty-three Hartley guinea pigs weighing 250 to 350 g with a normal Preyer's reflex were used. The animals were anesthetized with diazepam (5 mg/kg, i.p. initially, followed by 2.5 mg/kg every 2 h) and fentanyl (0.32 mg/kg, i.m. initially, followed by 0.16 mg/kg every 30 min), and were then tracheotomized. Respiration was maintained with room air without a respirator. Each animal's head was rigidly fixed with a nontraumatic head holder (Narishige, SH-15, Japan). A catheter was placed in the left femoral artery and connected to a pressure transducer (Nihon Kohden, SEN-6102M, Japan) for measurement of systemic blood pressure. Another catheter was placed in the left external jugular vein for the administration of drugs. Body temperature was maintained at 37.5 ± 0.2°C with a heating pad (Baxter, K-20, USA). The bulla was opened by a ventral approach without disturbing the ossicles, and the mucosa overlying the cochlea was removed with cotton pledgets. Cochlear blood flow was measured with a non-contact laser flowmeter (see below). Cochlear blood flow and blood pressure were recorded on a thermal recorder (Graphtec, WR7400, Japan).

The care and use of the animals were approved by the Animal Welfare Committee of the Hamamatsu University School of Medicine.

2.2. Photochemically induced focal cochlear microcirculatory disorders

In this study, the cochlear microcirculatory disorders were induced by photochemical reaction between rose bengal and green light, which causes endothelial injury followed by platelet adhesion, aggregation and formation of a platelet and fibrin-rich thrombus at the site of the photochemical reaction (Watson et al., 1985; Umemura et al., 1990a; Asai et al., 1993). A solution of rose bengal (20 mg/kg) dissolved in saline was injected intravenously, after which the lateral wall of the second cochlear turn was illuminated for 10 min with 1 mm diameter focused green light (540 nm) supplied from a 75 W xenon lamp (Hamamatsu Photonics, L-3306-01A, Japan).

2.3. Non-contact laser blood flowmetry

Laser Doppler flowmetry provides a direct, non-invasive, dynamic and linear measurement of inner ear blood flow (Miller et al., 1984; Short et al., 1985). However, the conventional contact-type laser Doppler flowmeter is not appropriate for evaluating changes in cochlear blood flow in our animals, because the probe placed over the lateral wall of the cochlea would hinder the green light illumination. Therefore we used a non-contact laser flowmeter (Neuroscience, FLO-N1, Japan) which uses polarized laser light to eliminate reflection from the tissue surface, and an electronic circuit with a fast time constant for stable and complete measurement of tissue blood flow (Kashima, 1994). Our previous studies confirmed that it is as applicable for monitoring cochlear blood flow change as the conventional contact type laser Doppler flowmeter (Iwasaki et al., 1998). In addition, cochlear vascular conductance was calculated from the ratio of cochlear blood flow to blood pressure (cochlear vascular conductance = cochlear blood flow/blood pressure). Cochlear vascular conductance allows the evaluation of the changes in cochlear blood flow that are not directly related to systemic blood pressure changes (Didier et al., 1993; Ren et al., 1993; Brechtelsbauer et al., 1994). As we previously reported that the impairment of cochlear blood flow in this model is mild (Iwasaki et al., 1998), a change in blood pressure is thought to be involved in the effects of drugs on changes in cochlear blood flow. Thus, we used the cochlear vascular conductance to evaluate the change in cochlear blood flow under the minimal influence of changes in blood pressure.

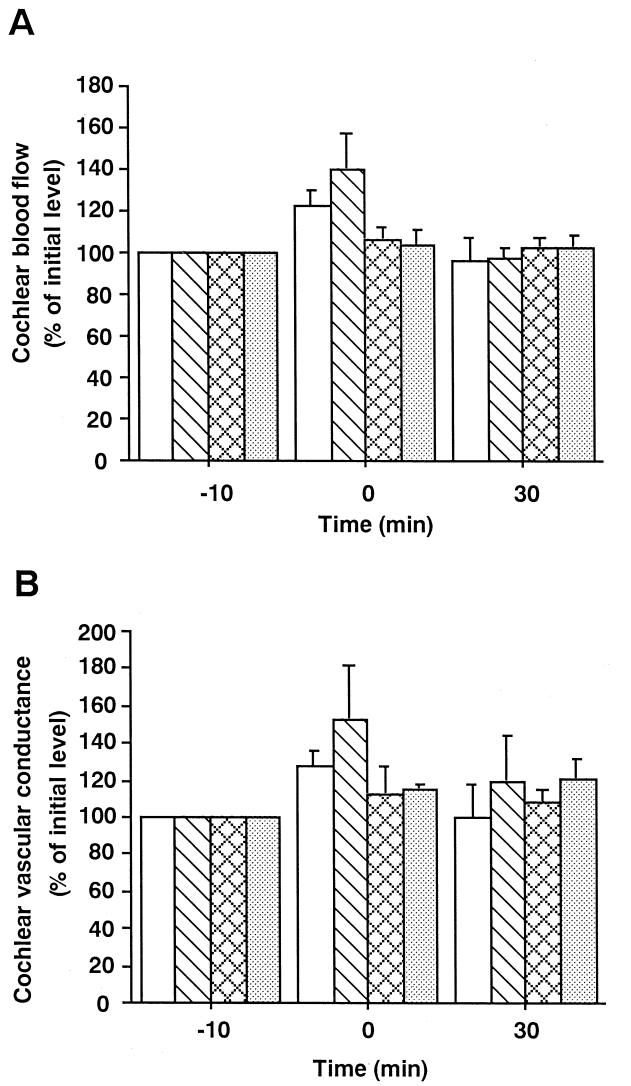

Fig. 1. Changes in cochlear blood flow (A) and cochlear vascular conductance (cochlear blood flow/blood pressure) (B) in control group B. A 10-min infusion of amidotrizoate (600 mg/kg) (open column, $n=3$), ATP (4 mg/kg) (hatched column, $n=3$), hydrocortisone (50 mg/kg) (crossed-hatched column, $n=3$) and hydrocortisone (100 mg/kg) (stippled column, $n=3$) caused increases in cochlear blood flow of $122.2\pm7.5\%$, $140.5\pm17.5\%$, $105.7\pm7.2\%$ and $104.4\pm6.4\%$ and increases in cochlear vascular conductance of $128.3\pm8.1\%$, $152.3\pm29.0\%$, $113.0\pm15.0\%$ and $115.3\pm2.4\%$ from the initial baseline level, respectively. Thirty minutes after completion of infusion, cochlear blood flow for each drug had decreased to $96.7\pm10.6\%$, $97.2\pm5.2\%$, $102.9\pm4.7\%$ and $102.1\pm6.3\%$ and cochlear vascular conductance had decreased to $100.7\pm18.0\%$, $119.3\pm24.8\%$, $108.0\pm6.9\%$ and $120.5\pm11.8\%$ of the baseline level, with no significant difference between them. Values are means $\pm$ S.E.M.

2.4. Experimental protocols

To evaluate the effect of various drugs on cochlear microcirculatory disorders, 0.8 ml/kg of saline (group A, $n=6$), 600 mg/kg of amidotrizoate (group B, $n=6$), 4 mg/kg of ATP (group C, $n=6$), 50 mg/kg of hydrocortisone (group D, $n=5$) and 100 mg/kg of hydrocortisone (group E, $n=5$) were administered by intravenous infusion 10 min before the start of the photochemical reaction. Dosages of amidotrizoate and ATP were determined to be maximum for clinical use (Morimitsu et al., 1977; Ushisako and Morimitsu, 1988; Brook et al., 1994; Redleaf et al., 1995; Miyata et al., 1997). In our preliminary study, the effects of these drugs in these dosages were confirmed to exceed the effect of hydrocortisone on the increase in cochlear blood flow. As controls, cochlear blood flow and blood pressure were measured after dye injection only ($n=3$), or illumination only ($n=3$) (control group A). The same doses of hydrocortisone ($n=3$ for each dosage), amidotrizoate ($n=3$) and ATP ($n=3$) were administered without rose bengal injection or illumination (control group B). Cochlear blood flow and blood pressure were continuously recorded for 30 min.

2.5. Morphological study

Seventy min after the start of the photochemical reaction, temporal bones were dissected and perfused with 2.5% glutaraldehyde in 0.1 M phosphate buffer at pH 7.4 via the round and oval windows. Cochleae were further post-fixed in 1% osmium tetroxide for 1 h and dehydrated in ethanol for electron microscopy. For observation by scanning electron microscopy (Hitachi, S-800, Japan), specimens were freeze-dried and sputter-coated with gold.

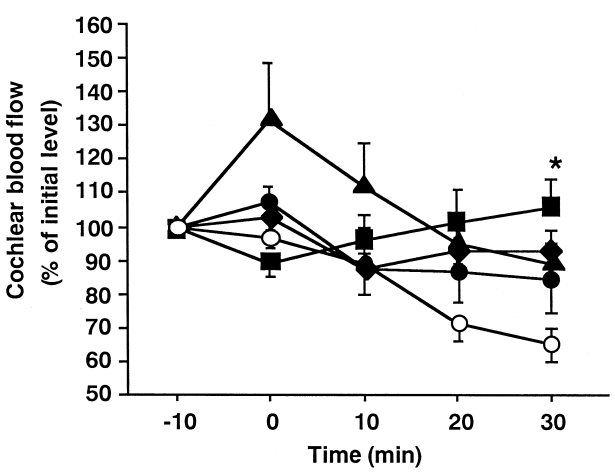

Fig. 2. Effects of 600 mg/kg of amidotrizoate (group B, closed circle, $n=6$), 4 mg/kg of ATP (group C, closed triangle, $n=6$), 50 mg/kg of hydrocortisone (group D, closed rhombus, $n=5$) and 100 mg/kg of hydrocortisone (group E, closed square, $n=5$) on the cochlear blood flow impairment induced by the photochemical reaction. In group A (saline, open circle, $n=6$), cochlear blood flow gradually decreased to $65.1\pm4.9\%$ of the initial baseline level 30 min after the onset of the photochemical reaction. In groups B, C, D and E, cochlear blood flow was $84.1\pm9.6\%$, $89.1\pm6.1\%$, $93.1\pm5.5\%$ and $105.6\pm8.3\%$ of baseline, respectively. Values are means $\pm$ S.E.M. Comparison vs. group A: $*$ $P<0.05$.

2.6. Statistical analysis

Repeated measure analysis of variance (ANOVA) was used to evaluate differences among groups in cochlear blood flow, blood pressure and cochlear vascular conductance. One-factor ANOVA was used to evaluate differences among groups in the extent of degeneration of the stria vascularis. All data are expressed as mean ± S.E.M.

3. Results

In control group A, neither dye injection alone nor illumination alone produced any significant changes in cochlear blood flow or blood pressure.

In control group B, 10 min infusion of amidotrizoate, ATP and hydrocortisone in two different doses (50 mg/kg, 100 mg/kg) produced increases in cochlear blood flow of 122.2 ± 7.5%, 140.5 ± 17.5%, 105.7 ± 7.2% and 104.4 ± 6.4% (Fig. 1A) of baseline, respectively, and increases in cochlear vascular conductance of 128.3 ± 8.1%, 152.3 ± 29.0%, 113.0 ± 15.0% and 115.3 ± 2.4% of baseline (Fig. 1B), respectively. Thirty minutes after completion of infusion, cochlear blood flow for had decreased to 96.7 ± 10.6%, 97.2 ± 5.2%, 102.9 ± 4.7% and 102.1 ± 6.3% of baseline for each drug (Fig. 1A) and cochlear vascular conductance values had decreased to 100.7 ± 18.0%, 119.3 ± 24.8%, 108.0 ± 6.9% and 120.5 ± 11.8% (Fig. 1B) of the baseline level. Ten minutes of infusion of ATP resulted in a transient large increase in cochlear blood flow and cochlear vascular conductance; however, there was no significant difference in cochlear blood flow or cochlear vascular conductance between each drug 30 min after completion of infusion.

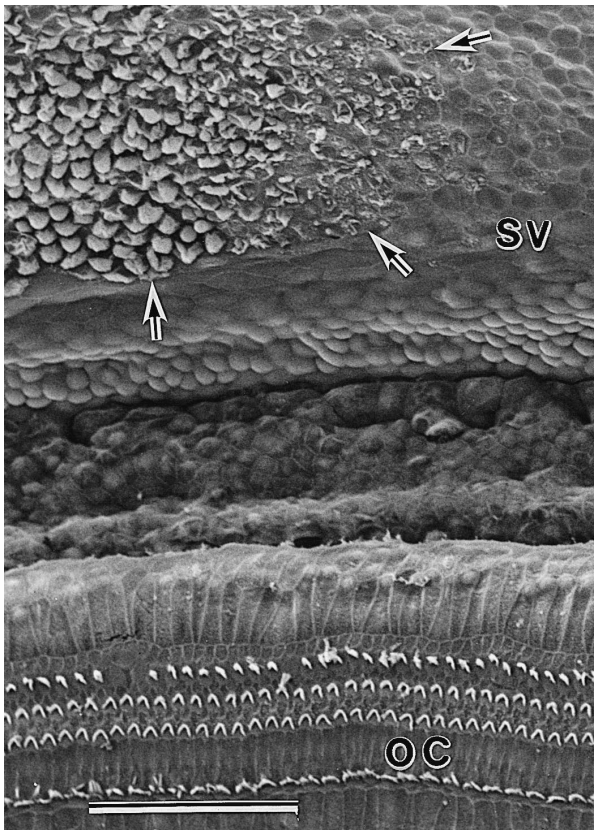

Fig. 4. Photochemically induced focal degeneration (arrows) of the stria vascularis (SV) in group A 70 min after the start of illumination. In contrast to the severe degeneration of the stria vascularis, the sensory hair cells on the organ of Corti (OC) facing the strial lesion remained intact. Scale bar = 100 μm.

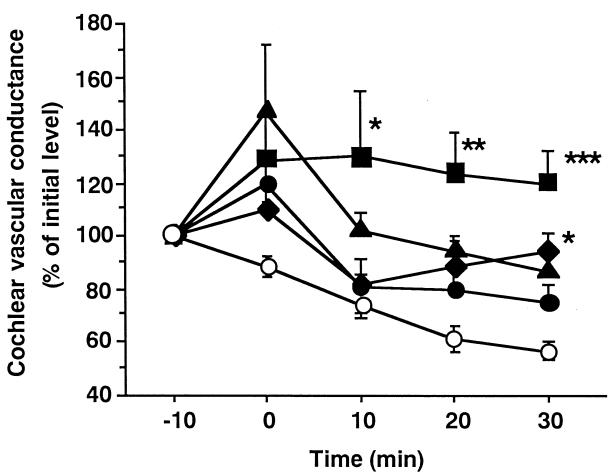

Fig. 3. Effects of 600 mg/kg of amidotrizoate (group B, closed circle, $n = 6$), 4 mg/kg of ATP (group C, closed triangle, $n = 6$), 50 mg/kg of hydrocortisone (group D, closed rhombus, $n = 5$) and 100 mg/kg of hydrocortisone (group E, closed square, $n = 5$) on the impairment of cochlear vascular conductance induced by the photochemical reaction. Cochlear vascular conductance gradually decreased to 57.0 ± 3.7% of the baseline level 30 min after the start of the photochemical reaction in group A (saline, open circle, $n = 6$). In groups B, C, D and E, cochlear vascular conductance decreased to 74.7 ± 6.7%, 86.5 ± 5.5%, 94.6 ± 6.3% and 119.7 ± 12.6% of baseline, respectively. Values are means ± S.E.M. Comparison vs. group A: $* P < 0.05$, $** P < 0.01$, $*** P < 0.001$.

In groups A, B, C, D and E, mean baseline systemic blood pressure was 53.3 ± 5.9 mmHg, 47.5 ± 3.4 mmHg, 54.2 ± 9.4 mmHg, 48.0 ± 2.7 mmHg and 58.6 ± 5.3 mmHg, respectively, with no significant differences between the groups. In group A, cochlear blood flow gradually dropped to 65.1 ± 4.9% of the initial baseline level 30 min after the start of the photochemical reaction. In groups B, C, D and E, cochlear blood flow was 84.1 ± 9.6%, 89.1 ± 6.1%, 93.1 ± 5.5% and 105.6 ± 8.3% of baseline, respectively. Hydrocortisone (100 mg/kg) prevented significantly the decrease in cochlear blood flow ($P < 0.05$) (Fig. 2). The other three drugs prevented the decrease in cochlear blood flow but not significantly ($P = 0.297$, 0.134 and 0.081, respectively).

Cochlear vascular conductance gradually decreased to 57.0 ± 3.7% of the baseline level 30 min after the start of the photochemical reaction in group A. In groups B, C, D and E, cochlear vascular conductance decreased to 74.7 ± 6.7%, 86.5 ± 5.5%, 94.6 ± 6.3% and 119.7 ± 12.6%, re-

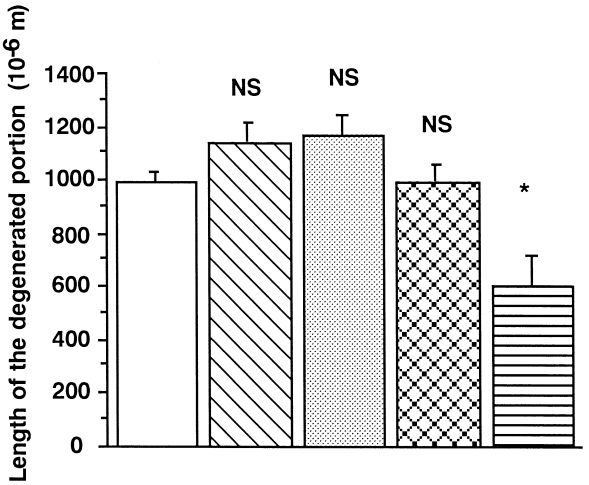

Fig. 5. The length of the degenerated portion of the stria vascularis in group A (saline, open column, $n = 5$), B (600 mg/kg of amidotrizoate, hatched column, $n = 5$), C (4 mg/kg of ATP, stippled column, $n = 5$), D (50 mg/kg of hydrocortisone, cross-hatched column, $n = 5$) and E (100 mg/kg of hydrocortisone, striped column, $n = 5$). In groups A, B, C, D and E, the length of the degenerated portion of the stria vascularis was 992.8 ± 39.6 μm, 1135.5 ± 82.9 μm, 1167.5 ± 80.7 μm, 989.1 ± 70.1 μm and 602.1 ± 116.0 μm, respectively. Values are means ± S.E.M. Comparison vs. group A: $* P < 0.01$.

spectively. Intravenous injection of hydrocortisone (50 mg/kg and 100 mg/kg) was found to prevent significantly the impairment of cochlear vascular conductance ($P < 0.05$ and $P < 0.001$, respectively) (Fig. 3).

Scanning electron microscopy revealed a degeneration of the stria vascularis in all experimental groups. Fig. 4 shows a scanning electron micrograph of the stria vascularis and organ of Corti 70 min after the start of the photochemical reaction in one animal of group A. In contrast to severe degeneration of the stria vascularis, the sensory hair cells on the organ of Corti facing the strial lesion remained intact. In groups A, B, C, D and E, the length of the degenerated portion of the stria vascularis was 992.8 ± 39.6 μm, 1135.5 ± 82.9 μm, 1167.5 ± 80.7 μm, 989.1 ± 70.1 μm and 602.1 ± 116.0 μm, respectively. Hydrocortisone (100 mg/kg) significantly reduced the length of the degenerated portion of the stria vascularis ($P < 0.01$) (Fig. 5).

4. Discussion

Various authors have reported the effects of drugs on cochlear blood flow (Kawakami et al., 1989; Quirk et al., 1990; Umemura et al., 1990b), and various techniques have been used to induce cochlear microcirculatory disorders (Short et al., 1985; Umemura et al., 1990a; Asai et al., 1993); however, no pharmacological studies have been carried out to investigate the effects of drugs on the focal decrease in cochlear blood flow. In previous studies, we investigated the morphological and physiological changes accompanying reactive oxygen species-induced focal microcirculatory disorders in the cochleae of guinea pigs (Iwasaki et al., 1997; Miyashita et al., 1998). In the present study, we tested the effect of various drugs on cochlear blood flow, using the same model.

In group A animals (saline), cochlear blood flow gradually decreased during the experimental period and never recovered to baseline level throughout the 1- to 2-h observation period. This pattern of cochlear blood flow change is obviously different from that seen in the conventional internal auditory artery occlusion method, which produces a rapid and severe decrease in cochlear blood flow (Short et al., 1985). Gradual and mild thrombogenesis is expected to occur in the focal lesion.

Amidotrizoate (diatrizoate) is a hyperosmolar ionic contrast medium. The effects of amidotrizoate on the circulatory system are controversial. Some authors reported that amidotrizoate had a vasodilator and anticoagulant effect (Rasuli et al., 1989; Gabriel et al., 1991; Baile et al., 1995), whereas other researchers reported that amidotrizoate reduced the number of perfused microvessels (Krause et al., 1994) and caused the aggregation of red cells (Liss et al., 1996). In this study, pretreatment with amidotrizoate (group B) did not significantly prevent the decrease in cochlear blood flow or cochlear vascular conductance. Although amidotrizoate was used in one dose of 600 mg/kg, this dose is the maximum dose used for the treatment of sudden sensorineural hearing loss, as described in Section 2. Bakris et al. (1990) reported that a high dose of amidotrizoate generated reactive oxygen species. Thus, a high dose of amidotrizoate is not suitable for evaluating pharmacological efficacy in this model. In some clinical studies of amidotrizoate treatment for sudden sensorineural hearing loss, improvement rates were found to be higher than spontaneous recovery rates (Morimitsu et al., 1977; Ushisako and Morimitsu, 1988; Redleaf et al., 1995). Morimitsu et al. (1977) described that in sudden deafness the blood cochlear barrier might be broken down and amidotrizoate may fill the broken membrane pores and activate the sodium pump again to produce normal endolymph. If amidotrizoate does have some effect in the treatment of sudden sensorineural hearing loss, it is unlikely that this includes increasing cochlear blood flow or scavenging reactive oxygen species.

The vasodilator effect of ATP is mediated by the endothelium and follows the release of nitric oxide (Janigro et al., 1996). Pretreatment with ATP (group C) resulted in a large increase in cochlear blood flow and a decrease in blood pressure which seemed to be caused by the vasodilator actions of ATP. ATP was used in a clinically maximum dose; a higher dose is thought to cause non-physiological effects. ATP also prevented the decrease of cochlear blood flow and the cochlear vascular conductance, but this effect proved to be not significant ($P = 0.2321$ and $P = 0.0935$, respectively). In addition, scanning electron microscopy of

the stria vascularis revealed no significant differences in the length of the degenerated area between group C and group A. In our previous study, we reported that only capillaries of the stria vascularis were affected during the acute phase, while the integrity of the spiral ligament vessels in the cochlear lateral wall was preserved (Iwasaki et al., 1997; Miyashita et al., 1998). Cochlear blood flow represents blood flow in the cochlear lateral wall vessels (Miller et al., 1984), including the stria vascularis and the spiral ligament. ATP may act to prevent the impairment of cochlear blood flow by increasing cochlear blood flow in the intact vessels, such as vessels of the spiral ligament adjacent the focal lesion.

Hydrocortisone is a corticosteroid which is widely used in the treatment of sudden sensorineural hearing loss on the basis of its anti-inflammatory effect (Byl, 1984; Kallinen et al., 1997). Cole and Jahrsdoerfer (1988) concluded that steroids may be of benefit in patients with moderate hearing loss and that there are no contraindications to therapy. Of the three drugs tested, hydrocortisone was the most effective in attenuating the impairment of cochlear blood flow and cochlear vascular conductance (groups D and E). It significantly prevented the decrease in cochlear blood flow and cochlear vascular conductance in a dose-dependent manner. In this model, the cochlear blood flow impairment is caused by reactive oxygen species. Reactive oxygen species are thought to cause the peroxidation of lipids in the mitochondrial membrane (Goda et al., 1973) and the luminal surface of endothelial cells (Watson et al., 1985), and to induce thrombosis. Otamiri (1989) has reported that hydrocortisone is a nonenzymatic antioxidant, and that intravenous pretreatment with hydrocortisone prevents lipid peroxidation. These observations support the hypothesis that hydrocortisone has therapeutic potential for, not only improving tissue inflammation of the cochlea, but also attenuating the impairment of cochlear blood flow induced by reactive oxygen species. Moreover, hydrocortisone also reduced the size of the degenerated portion of the stria vascularis in a dose-dependent manner. Properly maintained cochlear blood flow over a longer period of time could prove to be effective in protecting strial cells from additional anoxic damage.

In conclusion, intravenous pretreatment with hydrocortisone, but not amidotrizoate or ATP, proved to be effective in preventing the decrease in cochlear blood flow and cochlear vascular conductance produced in this model. Hydrocortisone was more effective than vasodilators or other agents which increase cochlear blood flow in preventing the reactive oxygen species-induced decrease in cochlear blood flow. This might be due to the antioxidative effects of hydrocortisone. Reactive oxygen species are thought to cause various sensorineural hearing disorders, such as presbycusis (Seidman et al., 1996), noise-induced hearing loss (Yamane et al., 1995), and ototoxicity of aminoglycosides or cisplatin (Clerici et al., 1996). Thus, further studies with this model may be of benefit for the prevention or treatment of these sensorineural hearing disorders.

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