

Histamine-Induced Endolymphatic Hydrops

Taizo Takeda¹, Setsuko Takeda², Akinobu Kakigi^{3*}, Naoya Egami⁴, Rie Nishioka⁵, Natsumi Uehara³ and Ken-ichi Nibu³

¹Department of Otolaryngology, Nishinomiya Municipal Central Hospital, Japan

²Department of Otolaryngology, Nishinomiya City, Japan

³Department of Otolaryngology-Head & Neck Surgery, Kobe University, Graduate School of Medicine, Japan

⁴Department of Otolaryngology, Faculty of Medicine, The University of Tokyo, Japan

⁵Department of Otolaryngology, San-ai Hospital, Japan

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Corresponding author:

Akinobu Kakigi,
Department of Otolaryngology-Head & Neck Surgery, Kobe University, Graduate School of Medicine, 7-5-1 Kusunokicho Chuo-ku, Kobe, Hyogo 650-0017, Japan. Tel; +81-78-382-6024
Email: kakigia@gmail.com

ABSTRACT

Objective

To investigate whether a rise in plasma histamine levels causes endolymphatic hydrops.

Methods

Ten normal Hartley guinea pigs were used for quantitative assessment of the volumetric changes of the endolymphatic space of the cochlea. Five of them received subcutaneous injection of histamine dihydrochloride to the back (3 animals: 1 mg/kg, 2 animals: 5 mg/kg), and remaining 5 animals received a subcutaneous injection of physiological saline, served as control. One hour after the injection, animals were sacrificed, and both sides of temporal bones were removed for light microscopic study. For quantitative assessment of the change of cochlear endolymphatic space, the cross-sectional area of the scala media was measured in the mid-modiolar sections of the cochlea. In addition, plasma histamine levels one hour after the histamine injection (1 mg/kg) were examined in four normal animals.

Results

High plasma histamine level was confirmed to persist one hour after the histamine injection. Reissner's membrane was distended in all cochleae with a histamine injection. Quantitative analysis was conducted in ears without artificial deformation (6 histamine-injected ears and 10 control ears). In histamine-injected ears, the cross-sectional areas of the scala media increased compared to that of the control ears. One way ANOVA Tukey test supports that histamine injection causes the endolymphatic hydrops ($p < 0.01$ and $p < 0.001$ in 1 mg/kg and 5mg/kg, respectively).

Conclusion

Systemic elevation in plasma histamine levels could cause the over-production of the endolymph, resulting in the development of endolymphatic hydrops.

INTRODUCTION

Allergy-induced endolymphatic hydrops was first reported by Naito T in 1952 [1]. Although the detailed procedure was not described, application of inactive horse

serum or tuberculin into the middle ear should induce Endolymphatic Hydrops (EH) in guinea pigs pre-sensitized with these antigens [1,2]. Since mild EH appeared within 1 hour after the provocation [3], the mechanism underlying the development of Naito's EH is suspected to be immediate hypersensitivity reactions or type 1 allergy. Allergy-induced EH, in the development of which type 1 allergy is confirmed to participate, was reported by Ishikawa group [4]. Their experimental procedure is that 2,4-Dinitrophenylated-Ascaris (DNP-As) antigen was challenged or boosted into the inner ear via the facial nerve in guinea pigs pre-sensitized with this antigen. EH was remarked one day after the immune challenge, and also the granulated mast cells appeared in the endolymphatic sac of the immunized side. Therefore, the development of EH is thought to be due to type 1 (or immediate) hypersensitivity allergic reaction, although the development of EH seems to be relatively delayed. Furthermore, we found that not only local immune challenge but also systemic immune challenge with DNP-As produced EH in guinea pigs [5]. In this animal model, the degranulation of mast cells was also observed in the endolymphatic sac of both sides within 1 hour of the immune provocation with DNP-As. These experimental facts suggested that type 1 (or immediate) hypersensitivity allergic reaction in the inner ear plays an important role in the development of EH. Activated mast cells may secrete active chemical mediators, such as histamine, leukotriene, and prostaglandin, which can act on the inner ear tissues [6]. Indeed, premedication of H1 receptor antagonist inhibited the development of EH induced by local as well as by systemic immune challenges with DNP-As [7,8]. Since histamine receptors for H1, H2 and H3 have been confirmed to be expressed in the rabbit endolymphatic sac [9], it seems likely that histamine participates in the development of EH.

In the present study, the effect of subcutaneously-injected histamine on the endolymphatic volume was histologically investigated to ensure a possible role of histamine in the development of EH. In addition to this histological study, plasma histamine levels were examined in small number of animals to confirm that the subcutaneous injection of histamine induced a rise in plasma histamine level for considerable periods enough to produce some influence on the inner ear morphology. Because the half-life of histamine in plasma is

assumed to be very short (minutes) [10,11] through metabolism by two pathways, methylation by methyltransferase and oxidation by diamine oxidase [12]. Therefore, the locally-injected histamine threatens to be fairly rapidly degraded, and to have no influence on the inner ear.

MATERIALS AND METHODS

Plasma histamine levels

Four normal Hartley guinea pigs received subcutaneous injection of histamine hydrochloride to the back (Sigma-Aldrich Co. LLC. St. Louis, MO, USA) (1 mg/kg body weight). One hour after the injection, blood samples were collected around 10 a.m. as a rule, under light anesthesia by a muscular injection of xylazine (5 mg/kg) and ketamine (35 mg/kg). Animals were quickly decapitated at 0 min with the use of a guillotine and trunk blood was collected in plastic tubes containing EDTA-Na. The blood to be collected was not less than 10 ml. Blood samples were immediately centrifuged at 4°C and plasma was stored at -20°C. Plasma histamine concentrations were measured by a radioimmunoassay using histamine ELISA kit (Immunotech, Beckman Coulter Inc. CA, USA). The measurement of plasma histamine levels was conducted in SRL Inc. (Tokyo, Japan).

Volumetric Changes of the Scala Media

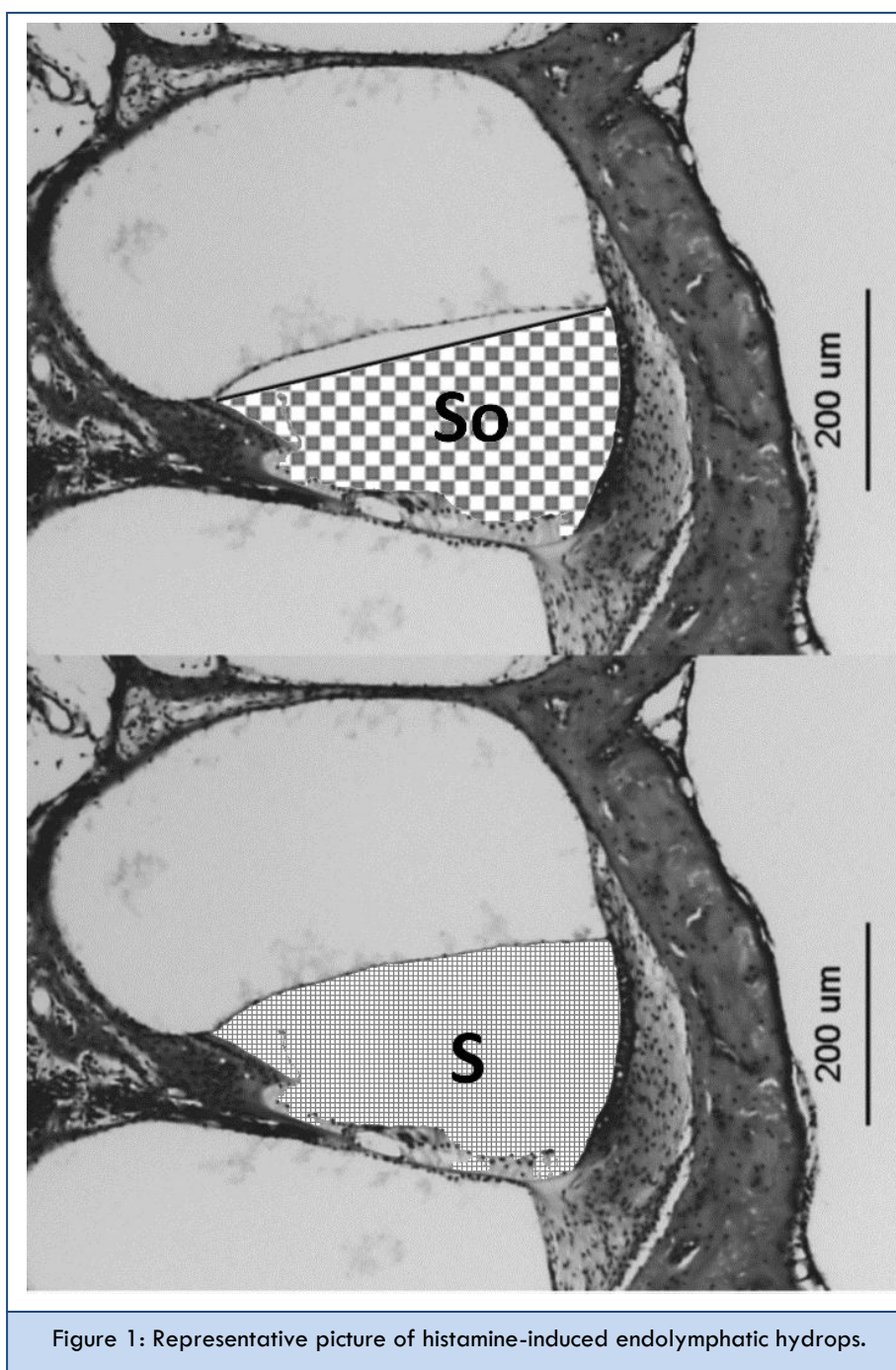
Ten normal Hartley guinea pigs were used for histologic study to examine histamine-induced volumetric changes of the scala media. Five of them received subcutaneous injection of histamine dihydrochloride to the back (3 animals: 1 mg/kg, 2 animals: 5 mg/kg), and remaining 5 animals received a subcutaneous injection of physiological saline, served as control. One hour after the injection, animals were sacrificed and perfused with physiological saline solution and fixed the temporal bones with 10% formalin (4.0% formaldehyde) under deep anesthesia with an intra-peritoneal injection of pentobarbital. Both sides of the temporal bones were removed and post-fixed in 10% formalin solutions for 10 days or more. Thereafter, they were decalcified with 5% trichloroacetic acid and dehydrated in a graded ethanol series. They were embedded in paraffin and celloidin. The prepared blocks were cut horizontally into 6 µm sections. The sections were stained with H&E and observed under a light microscope.

For quantitative assessment of the degree of EH, the cross-sectional area of the scala media was measured in the mid-

modiolar sections of the cochlea. The measurement was performed essentially as previously described [5]. Briefly, we used the following 2 parameters: (1) the cross-sectional area of the original scala media (S_o) (Figure 1), (checked area) and (2) the cross-sectional area of the dilated scala media (S) (Figure 1), (grating area). From these two parameters, we calculated the total increase ratios (IR; %) of the cross-sectional area of

the scala media, using the following formula: $\sum(S-S_o)/\sum S_o$ (%). The measuring system included a video camera, a computer, and a digitizer (Video Micro Meter VM-30; Olympus, Co., Tokyo, Japan).

The care and use of animals in this study were approved by the Kochi Medical School Animal Care and Use Committee.



Mild endolymphatic hydrops is evident in the cochlea of animals with a histamine injection.

RESULTS

Plasma Histamine Levels

Plasma histamine levels 1 hour after the subcutaneous injection of histamine chloride were 71, 77, 95, and 360 nM. Since normal histamine level is around 2 nM in guinea pigs [13], the results supported that high plasma histamine level still persisted 1 hour after the injection.

Increase Ratio of the cross-sectional area of the scala media

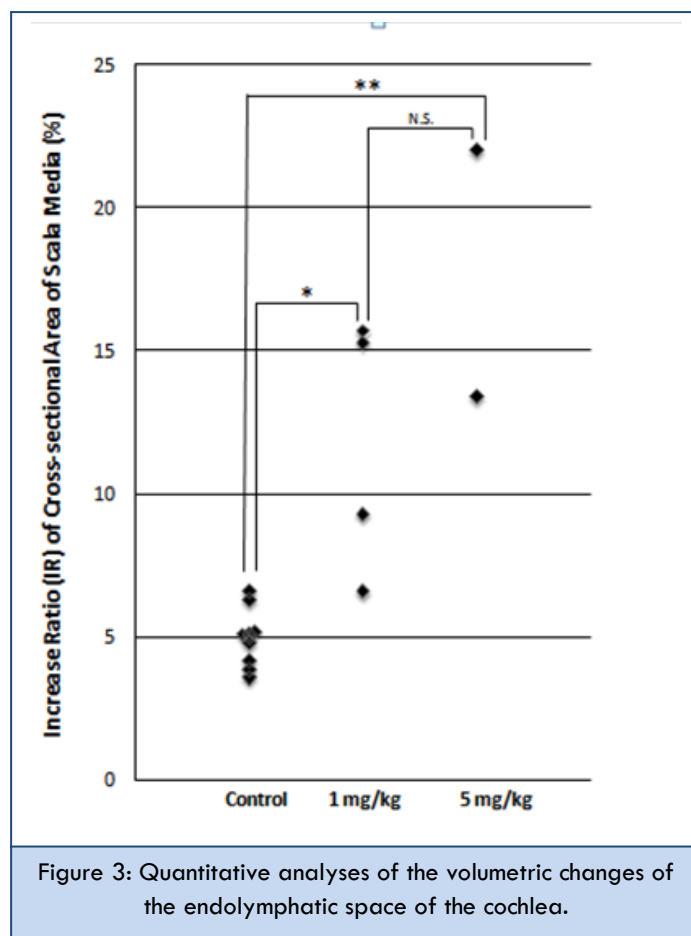
Reissner's membrane was distended in all cochleae with a histamine injection (Figure 2). But, artificial deformation (slightly ruptured Reissner's membrane in one ear, and deformed apex or basal turn in 3 ears) was found in 4 ears, so that these specimens were excluded from quantitative assessment of the

degree of EH. Meanwhile, there was no morphological problem in all tissue blocks of control ears with a saline injection.

Increase Ratio (IR) of control ears was 4.98 ± 0.90 % (n=10 ears). The IRs (%) of histamine-injected animals were 15.7, 6.6, 15.3, 9.3 % in the group with histamine dose of 1 mg/kg, and 13.4, 22.0 % in a group with the histamine dose of 5 mg/kg. Figure 3 represents a comparison of IRs between controls and histamine-injected animals. The IRs were significantly different between the control ears and histamine-injected ears (one way ANOVA Tukey test, $p < 0.01$ and $p < 0.001$ in 1 mg/kg and 5mg/kg, respectively). This result supports that histamine injection and its subsequent rise in plasma histamine level causes the endolymphatic hydrops.



The cross-sectional area of the original Scala Media (S_o) and the dilated scala media (S) is represented by checked area and grating area, respectively.



The Increase Ratios (IRs) of the cross-sectional area of the scala media were significantly different between the control ears and histamine-injected ears (one way ANOVA Tukey test, *: $p < 0.01$, **: $p < 0.001$)

DISCUSSION

The pathology of MD is well established to be endolymphatic hydrops. However, the mechanism underlying deafness and vertigo of MD or idiopathic EH is still unknown. Many possible etiologic factors lead to hydrops, and hydrops in turn generates the symptoms. However, this hypothesis of hydrops as being the final common pathway has not been proven conclusively [14]. Clinically, it is well known that mental and/or physical stress exacerbates MD. Recently, vasopressin that is one of stress hormones is closely associated with the formation of EH: (1) plasma levels of arginine VP are higher in patients with MD and may depend on the phase that the patient is in, [15-17] (2) acute and chronic application of arginine VP produces EH in guinea pigs and rats, [18-20] (3) V2 receptor mRNA is expressed in rat and human inner ear, [21-24] and (4) expression of V2 receptor mRNA in the rat inner ear is down-regulated by VP application. [25] Such accumulated evidence

has led to the assumption that production of endolymph is controlled by VP-AQP2 system. Concerning relationship between stress and MD, Calabrese, et al. have reported that oxidative stress is involved in the development of EH and that cellular damage and apoptotic cell death might contribute to the sensorineural hearing loss found in later stages of MD [26]. In this study, we investigated allergy induced EH that is one of possible etiologic factors because allergic reaction also causes some stress.

Concentrations of histamine in the blood and urine are normally very low, being less than 10 nM both in human and rodents of rats, mice and guinea pigs (about 7 nM in human [27,28], in rats [29], and around 2.0 nM in guinea pig [13] and mice [30]. Significant increases can be seen in people with a severe allergic reaction. For example, with allergy-induced anaphylaxis, blood histamine concentrations increase rapidly,

rising within 10 minutes of the start of symptoms and returning to normal within about 30 to 60 minutes [31]. Generally, a rapid degradation of histamine levels in the blood was well known because of the very short half-life time [32,33]. It is likely that subcutaneously injected histamine was rapidly metabolized and inactivated by methyltransferase and by diamine oxidase, especially in the present case without any pathological condition to persist a rise of histamine. In the pilot study, however, plasma histamine levels still remained high one hour after the injection.

EH was reported to develop both by local and by systemic allergic provocations with DNP-As [1-5]. Since the development of allergy-induced EH was suppressed by anti-histamine agents [8], there is little doubt that histamine is implicated in the over-formation of endolymph, resulting in EH. In the literature, there are a lot of reports about histaminergic nerve system in the inner ear, but a very little report about the role of histamine in the inner ear fluid homeostasis. According to Duvall's report [34], histamine application produced a time- and dose-dependent change in the rate of stria vascularis vessel permeability to a small protein tracer (horseradish peroxidase), but the basic ultra structure of the inner ear was not altered by histamine. The possible histamine-induced volumetric change of the scala media was first described by Uchida, et al [35]. They observed the behavioral vestibular function and morphological changes of the inner ear in guinea pigs with immunologically-obiterated endolymphatic sac after the intraperitoneal injection of histamine (1mg/kg). Vertiginous attack with spontaneous nystagmus was observed in 3 animals of 38 experimental animals, and postural deviations on a flat in 2 animals. Neither spontaneous nystagmus attacks nor postural deviations were observed in animals without the histamine injection. Morphologically, animals with a vertiginous attack developed distinct edema in the stria vascularis. Especially, a rupture of Reissner's membrane was observed in an animal with a severe vertiginous attack. Although the influence of histamine on the degree of EH was inconclusive because of qualitative assessment by Paparella's grading system [36], they speculated that histamine-induced vestibular disturbance was caused by the overproduction of endolymph in the stria vascularis. Allergy-induced vestibular disturbance of nystagmus and head deviation was observed in animals locally

immunized with DNP-Asc [4]. The manifestation of such vestibular disorders were suppressed by the premedication with tranilast or pemirolast potassium which inhibits the antigen-induced release of chemical mediators including histamine from mast cells [37,38], but the change of EH was not mentioned. As to the morphological change of EH, we already reported that type1 allergy-induced EH was also suppressed by the premedication of histamine H1-receptor antagonist [8]. Additionally, the present study showed that an increase of plasma histamine caused EH. These results indicate that histamine plays a potential role on the development of EH and its concomitant inner ear disorders.

In general, histamine exerts its effects by binding to G protein-coupled histamine receptors, designated H1 through H4. Via these receptors, histamine regulates various allergic reactions not only as a chemical mediator but also as a neurotransmitter [12]. Indeed, the symptoms resulting from intravenous injection of histamine are similar to those associated with anaphylactic shock and allergic reactions [39]. These include contraction of airway smooth muscle, stimulation of secretions, dilation and increased permeability of the capillaries, and stimulation of sensory nerve endings. Histamine receptors are known to be expressed in the inner ear. H1 receptor is reported to be expressed in both frog and mouse vestibular epithelia [40]. Further, H1, H2 and H3 receptors are expressed in the rabbit endolymphatic sac [9]. We also confirmed the same results in the rat endolymphatic sac (Figure 4) [5,41]. These areas are involved in the inner-ear fluid homeostasis [42]. In the cochlea, we found that H1, H2 and H3 receptors were expressed in the spiral ganglion cells [43], but could not find in the stria vascularis, another main site responsible for endolymph secretion. Anyway a rise in plasma histamine level scan have some influence on the inner-ear fluid homeostasis via these histamine receptors expressed in the inner ear. The development of EH shown in the present study is thought to be due to histamine-induced over-production of the endolymph via histamine receptors in the inner ear. Allergy have been thought as a causative or associated factor in the inner ear disorders, especially Meniere's disease or EH [44]. However, this hypothesis were mainly based on clinical documentation that vertigo, tinnitus, and hearing loss in Meniere's disease were improved after desensitization to inhalant allergens and an

elimination diet for food allergies, not on basic evidence. The present results experimentally support the hypothesis. It is likely

that an elevation of plasma histamine resulting from allergy responses, e.g. food allergy, causes Meniere's attack.

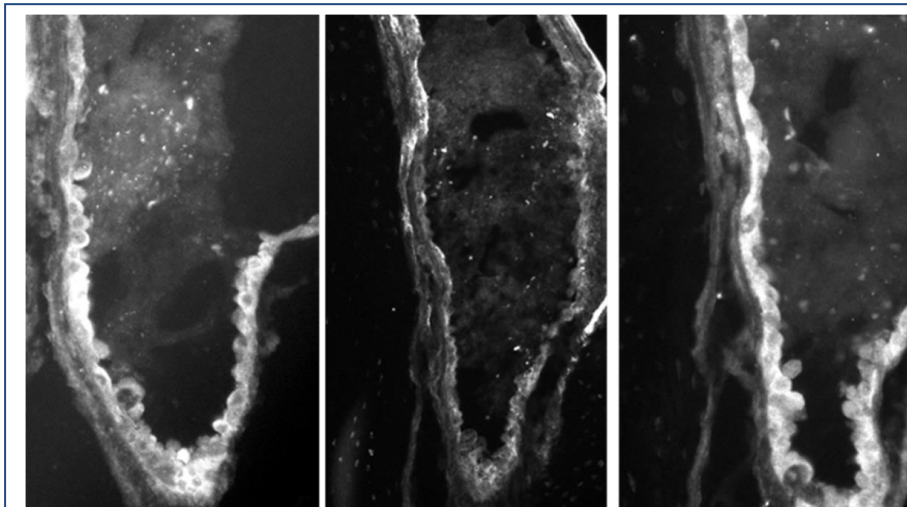


Figure 4: Immunoreactivity of H1, H2, and H3 in the endolymphatic sac.

H1, H2, and H3 receptors were expressed in the rat endolymphatic sac.

CONCLUSION

Systemic elevation in plasma histamine levels could cause the development of endolymphatic hydrops. The present results support the allergic aspect of Meniere's disease that food allergy or inhalant allergy may play a part.

DISCLOSURE STATEMENT

The authors are not aware of any conflict of interest or similar issue that may be relevant to the present work.

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