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The inner ear is a barometric pressure sensor—change in barometric pressure induces vestibular ganglion cell activation in mice

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This immunohistochemical study evaluated the activity of primary sensory neurons in the vestibular ganglion in response to lowered barometric pressure (LBP) in mice to assess whether changes in barometric pressure were perceived by the vestibular system. Mice were anesthetized and exposed to three consecutive barometric pressure drops within the range of natural weather variations (-20 hPa from the atmospheric pressure). Following anesthetization and paraformaldehyde perfusion 1-hour post-LBP exposure, activity-regulated cytoskeleton-associated protein (Arc) immunoreactive cells in the superior vestibular ganglion (SVG) and inferior vestibular ganglion (IVG) were counted bilaterally and compared with those of controls. In the positive control study, anesthetized mice were placed in the prone position and subjected to rotary motion (RM). The total number of Arc-positive neurons in the IVG, but not in the SVG, was significantly higher in LBP-exposed mice than in controls, regardless of sex. The total number of Arc-positive neurons in the SVG, but not in the IVG, was significantly higher in RM-stimulated mice than in controls. These data showed that primary sensory neurons in the IVG responded to LBP, strongly suggesting that changes in barometric pressure might be perceived by the saccule or posterior semicircular canal innervated by IVG neurons in mice.

Meteorological changes have long been considered a trigger for the onset of meteoropathies, such as headache and other chronic pain conditions[1–4]. Various meteorological factors, including air pressure, humidity, and temperature, have been suggested to affect pain[5–7]. We previously showed that lowering the barometric pressure within the range of natural weather variations using a climate chamber (5–27 hPa lower than atmospheric pressure) increased pain-related behavior in rats and mice with chronic constriction injury (CCI) of the sciatic nerve[8,9]. Additionally, we reported that barometric pressure-induced increases in pain-related behaviors were abolished by drug-induced destruction of the inner ear in CCI rats[10]. Further examination revealed that decreasing barometric pressure stimulation increased c-Fos immunoreactivity (i.e., cell activation) in the superior vestibular nucleus but not in the other vestibular nuclei, with no significant differences between male and female mice[11]. Neurons in the superior vestibular nucleus are known to receive inputs principally from the semicircular canals and otolith organs via the vestibular nerve[12–14], suggesting that a barometric sensor or sensing system might be located in these organs in mice. However, it remains unclear which organs in the inner ear are responsible for sensing barometric pressure. To address this, herein, we immunohistochemically assessed the activity of primary afferent neurons in the mouse superior and inferior vestibular ganglions (SVG and IVG, respectively) that responded to lowered pressure. Additionally, to verify the validity of the methodology used herein, we first conducted an experiment in which mice were subjected to rotary motion (RM) stimulation.

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Results

Activity-regulated cytoskeleton-associated protein (Arc) immunoreactivity after rotary motion (RM) stimulation

To verify the validity of the methodology used in the present study, we first conducted an experiment in which RM stimulation was applied to anesthetized female mice in the prone position. Figure 1 shows Arc-immunoreactivity in the SVG and IVG cells after RM stimulation. The photomicrographs in Fig. 1a (under control condition) and 1b (after RM stimulation) were obtained from SVG sections. The photomicrographs in Fig. 1c (under control condition) and 1 d (after RM stimulation) were obtained from IVG sections. Several SVG cells in the tissues of RM stimulation-exposed mice (Fig. 1b) exhibited Arc immunoreactivity. In contrast, SVG cells in the tissues of control mice (Fig. 1a) did not exhibit Arc immunoreactivity. The average number of Arc-immunoreactive cells was significantly greater in RM stimulation-exposed mice than in controls (Fig. 1e left; unpaired *t*-test, $p < 0.05$). In contrast, IVG cells in the tissues of both control (Fig. 1c) and RM stimulation-exposed (Fig. 1d) mice showed Arc immunoreactivity. The average number of Arc-immunoreactive cells in the IVG did not significantly differ between RM stimulation-exposed mice and controls (Fig. 1e right; unpaired *t*-test, $p = 0.79$). These results indicate that RM stimulation activated SVG neurons, which mainly transmitted rotational sensations from the anterior and lateral semicircular canals[12–14]. Based on these findings, the immunohistochemical technique used in this study was considered to adequately evaluate the activity of the primary afferent nerves in the vestibular ganglia.

Arc immunoreactivity after Lowered barometric pressure (LBP) stimulation

Figure 2 shows Arc-immunoreactivity in SVG and IVG cells of both male and female mice after LBP stimulation. The photomicrographs in Figs. 2a (under control condition) and 2b (after LBP stimulation) were obtained from SVG sections of mice. SVG cells in both control and LBP-exposed mice did not exhibit Arc immunoreactivity. Conversely, some IVG cells in the tissues of both control (Fig. 2c) and LBP-exposed mice (Fig. 2d) exhibited Arc immunoreactivity. The average number of Arc-immunoreactive cells in the IVG was significantly affected by barometric pressure (Fig. 2e right, two-way analysis of variance; F1, 30 = 9.76, $p < 0.01$) but not sex. No significant interaction was observed between barometric pressure and sex. Post hoc Tukey–Kramer test indicated

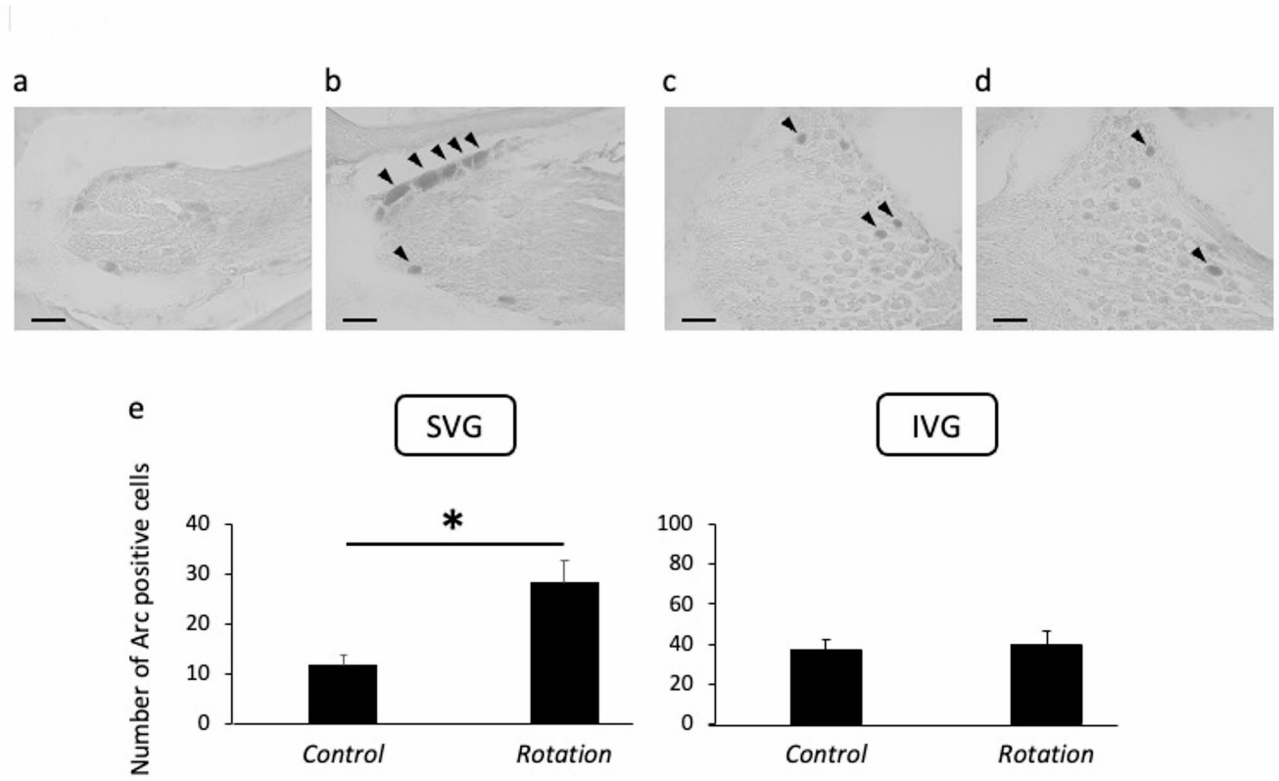

Fig. 1. Arc immunoreactivity in the superior vestibular ganglion (SVG) and inferior vestibular ganglion (IVG) cells after rotary motion (RM) stimulation. All optic micrographs (**a**–**d**) were obtained using a digital microscope (magnification: 400×). Scale bars in each micrograph represent 40 µm. (**a**) The micrograph of the SVG in a mouse under control conditions. (**b**) The micrograph of the SVG in a mouse after RM stimulation. Arrowheads indicate Arc-positive cells. (**c**) The micrograph of the IVG in a mouse under control conditions. Arrowheads indicate Arc-positive cells. (**d**) The micrograph of the IVG in a mouse after RM stimulation. Arrowheads indicate Arc-positive cells. (**e**) Numbers of Arc-positive cells in the SVG and IVG in female mice after RM stimulation (*Rotation: n* = 8) or under control conditions (*Control: n* = 8). Each bar represents the mean ± standard error, * $p < 0.05$ (unpaired *t*-test).

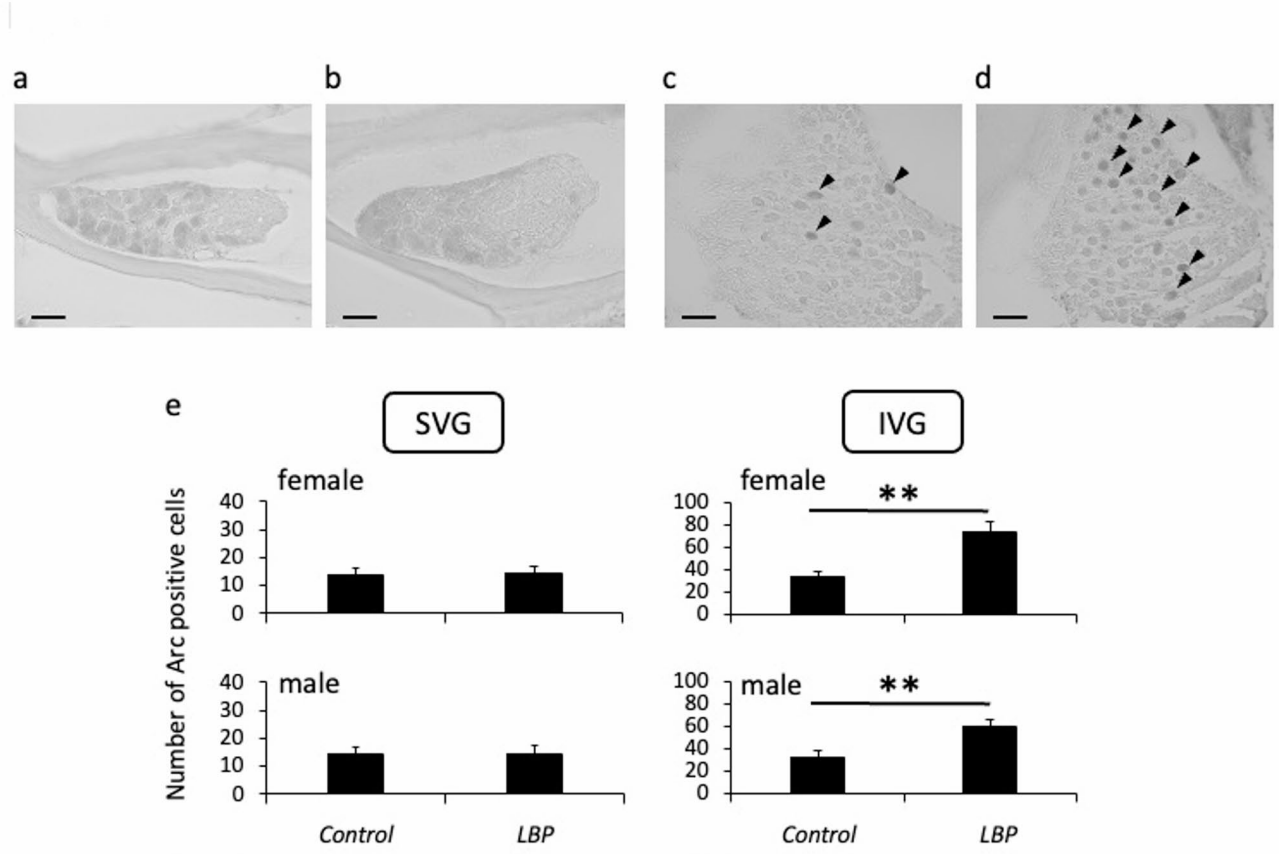

Fig. 2. Arc immunoreactivity in the superior vestibular ganglion (SVG) and inferior vestibular ganglion (IVG) cells after lowered barometric pressure (LBP) stimulation. All optic micrographs (a–d) were obtained using a digital microscope (magnification: 400×). Scale bars in each micrograph represent 40 µm. (**a**) The micrograph of the SVG in a mouse under control conditions. (**b**) The micrograph of the SVG in a mouse after LBP stimulation. (**c**) The micrograph of the IVG in a mouse under control conditions. Arrowheads indicate Arc-positive cells. (**d**) The micrograph of the IVG in a mouse after LBP stimulation. Arrowheads indicate Arc-positive cells. (**e**) Number of Arc-positive cells in the SVG and IVG in female and male mice after LBP stimulation (*LBP:* $n = 8$ females, $n = 8$ males) or under control conditions (*Control:* $n = 8$ females, $n = 8$ males). Each bar represents the mean ± standard error, ** $p < 0.01$ (Tukey–Kramer test).

that LBP stimulation significantly increased the average number of Arc-immunoreactive cells in the IVG of both sexes ($p < 0.01$). In contrast, the average number of Arc-immunoreactive cells in the SVG was not significantly affected by the barometric pressure or sex (Fig. 2e left). These results showed that LBP stimulation increased Arc immunoreactivity in IVG neurons, which receive input principally from the saccule and posterior semicircular canal[12–14]. These data suggest that barometric sensors may be located in the saccule and/or posterior semicircular canal in mice.

Discussion

This study aimed to examine whether barometric pressure changes within the range of natural weather variations affected the activity of primary neurons in the mouse vestibular ganglion. To assess this, the total number of Arc-immunoreactive cells in the SVG and IVG was counted bilaterally by an experimenter blinded to the experimental conditions. To verify the validity of the methodology used in the present study, we first conducted an experiment in which RM stimulation was applied to anesthetized mice in the prone position. As expected, horizontal RM stimulation activated the SVG cells, which mainly transmitted rotational sensations from the anterior and lateral semicircular canals. The plane of RM stimulation may explain the immunoreactivity observed in the SVG but not IVG. It is likely that the RM stimulation primarily influenced the horizontal canal plane, which would not activate structures or afferents associated with IVG. Based on these results, the immunohistochemical technique used in this study was considered to adequately evaluate the activity of the primary afferent nerves in the vestibular ganglia. Our data demonstrate that distinct neurons in the IVG respond to LBP stimuli. These data are consistent with our previous observation that secondary afferent neurons in the superior vestibular nucleus of the mouse brain stem, which mainly receive input from IVG cells, respond to lower barometric pressure[11].

In the present experiment, all animals were anesthetized and immobilized to minimize inputs to the inner ear due to body movement. The three-drug anesthesia mixture used in the present study has been demonstrated

to suppress the activity of the autonomic nervous system in mice[15]. However, to our knowledge, no studies have reported vestibular nervous system suppression associated with the use of this anesthetic method. Furthermore, in the tissue specimens analyzed in this study, many cells in the cochlear ganglion were Arc-immunoreactive, while few cells in the cerebral cortex were Arc-immunoreactive (data not shown), suggesting that the anesthetic approach used in this study likely did not suppress inner ear function.

Suzuki et al. reported that pressure changes in the middle ear of guinea pigs induced a pressure difference between the perilymph and endolymph, leading to an increase in vestibular nerve activity[16–18]. It is reasonable to assume that LBP stimulation induces a relative overpressure in the middle ear cavity, thereby inducing neural activity in the vestibular ganglia. This hypothesis is supported by the fact that the activity of experimental mice changes in response to natural barometric pressure changes, suggesting that mice can sense barometric pressure changes[19]. Nonetheless, the present study leaves several questions unanswered. As mentioned previously, we considered that LBP stimulation might induce pressure changes in the middle ear or a pressure difference between the perilymph and endolymph. However, no associated SVG activation or excitability in either ganglia or other sensory structures was observed. At present, we do not have definitive explanations for these observations. One possibility is that the pressure sensor may be located in the saccule, given its mechanosensitive properties. In addition, because the saccule is located just behind the oval window[12–14], which is easily exposed to changes in external air pressure, it may react to even small fluctuations in air pressure. Indeed, in people whose pain is affected by the weather, symptoms worsen due to small fluctuations in barometric pressure that precede changes in weather rather than to the large changes in barometric pressure that accompany it[20].

One important question concerns the contribution of this induced activity in vestibular sensory neurons to the perception of changes in barometric pressure. The sacculus largely induces reflexes. Thus, it remains unclear how these changes might impact routine saccular function or whether they are modulated by efferent feedback. Dose-dependent otolith deficits following noise exposure have been demonstrated in animal models[21]. This observation suggests that changes in barometric pressure may suppress routine saccular function, enabling the perception of changes in air pressure as a sensation. This hypothesis can be tested by testing vestibular functions or vestibular sensory-evoked potential, which is associated with the sacculus. In the present experiment, control animals were subjected to RM stimulation. However, using jerk stimulation of otolith organs, such as in vestibular sensory-evoked potential, may be more relevant for this purpose, which could allow for a comparison of subclasses of vestibular neurons.

Taken together, the current data suggest the presence of a barometric sensing system in the inner ear that alerts mice to atmospheric pressure. Barosensing has long been known as a common phenomenon in vertebrates[22,23]. Birds sense barometric pressure using a mechanoreceptor in the middle ear, the paratympanic organ (PTO)[24]. The PTO, which functions as both a barometer and an altimeter, is thought to help birds detect changes in weather and altitude during migration. In birds, the PTO is innervated by the facial nerve and projects to the vestibular nuclei[25], which may mediate pressure perception[26]. In humans, a similar system to detect small changes in air pressure has not been identified. However, it has been reported that sudden, large changes in air pressure during diving and flight can sometimes cause a transient, reversible dizziness[27,28]. In addition, we previously reported that weather-sensitive patients with migraines showed lower thresholds for self-motion perception in response to galvanic vestibular stimulation[29]. Despite different innervation (facial nerves vs. the vestibular ganglion), similarities in function (pressure sensing) and projections (the vestibular nuclei) suggest convergent evolution in birds and humans.

The present study showed that LBP stimulation increased Arc immunoreactivity in the IVG but not in the SVG. There was no significant difference in the number of Arc-immunoreactive cells in the IVG between male and female mice. These results were consistent with the findings of our previous study, in which we observed no significant difference in the increase in cellular c-Fos immunoreactivity in the superior vestibular nucleus due to LBP stimulation between male and female mice[11].

Neurons in the IVG receive inputs principally from the saccule and posterior semicircular canals[12–14]. On the other hand, neurons in the SVG receive inputs principally from the utricle and both the anterior and horizontal canals[12–14]. These observations suggest that barometric sensors may be located in the saccule and/or posterior semicircular canal in mice. Further studies are required to elucidate the pressure-sensing mechanism underlying this system.

The mechanism by which the excitation of the vestibular nervous system causes weather-related illnesses remains unknown. We considered the following possibilities.

First, the effects of vestibular nerve activity on autonomic function through the modulation of the brainstem autonomic center may affect sympathetic nerve activity[30,31]. We have previously shown that LBP increases blood pressure and heart rate in normal rats[32]. Furthermore, we reported that LBP increased the blood pressure and heart rate in weather-sensitive patients[29]. These results suggest that changes in barometric pressure induce sympathetic activation in both animals and humans. The effects of sympathetic nerve activity on pain afferents after nerve injury have been well reported[33–35]. Furthermore, sympathectomy suppresses the aggravation of mechanical hyperalgesia induced by LBP stimulation in CCI rats, suggesting that sympathetic nerve activity is involved in this phenomenon[8]. Based on these findings, we speculate that vestibular nerve activation induced by LBP stimulation increases pain via sympathetic nerve activity.

Second, vestibular nerve activity may induce hormonal changes. This hypothesis is based on previous reports that neurons in the vestibular nuclei project to the hypothalamus and may regulate the hypothalamic-pituitary-adrenal axis (HPA axis) in rats[36] and humans[37]. It is well known that several chronic pain disorders are associated with the HPA axis[38–40], and catecholamines are considered to be released from the adrenal medulla in response to LBP stimulation. We recently found that the plasma corticosterone levels in CCI mice significantly increased after three consecutive LBPs at 20 hPa[41]. These findings suggest that the HPA axis activation may play an important role in LBP-induced pain in mice. These circulating hormones may directly activate peripheral

nociceptive fibers and induce vasoconstriction, resulting in increased pain. Cutaneous nociceptive fibers are known to respond to adrenaline and noradrenaline following nerve injury[33,35,42].

Third, excitation of the vestibular nerve causes excitation of the trigeminal nerve. The vestibular and trigeminal nerves share mutual neural connections[43]. It is a well-known fact that when the trigeminal nerve becomes excited due to changes in temperature, light, odors, etc., calcitonin gene-related peptide is released from the terminals, which causes increased permeability and vasodilation of the dural blood vessels; these inflammatory changes further excite the trigeminal nerve, resulting in a migraine attack[44]. It is conceivable that barometric pressure changes excite the vestibular nerve, which in turn excites the trigeminal nerve, causing migraines. The aforementioned hypotheses are reasonable based on previous literature; however, direct experimental verification is required in future studies.

This study has some limitations. First, it was a simple histopathological examination of the effects of LBP on the activity of vestibular ganglion neurons, relying on Arc expression as a correlative marker of activity rather than direct functional recording (e.g., electrophysiology). Moreover, the specific mechanosensitive cells and molecular transducers within the inner ear remain unidentified. Second, the experiments were performed under anesthesia, which may differ from the physiology of the conscious state.

In conclusion, the present study showed that neurons in the IVG respond to changes in barometric pressure. Similar mechanisms may contribute to the development of meteoropathies induced by changes in barometric pressure in humans.

Methods

Animals

All experiments were performed between 09:00 and 13:00 in accordance with the Guidelines for Animal Experiments of Chubu University and Aichi Medical University, ARRIVE guidelines (Animal Research: Reporting of in Vivo Experiments), and the IASP Guidelines for the Use of Animals in Research. All animal experiment protocols were approved by the Animal Experiment Committees of Chubu University (202410004) and Aichi Medical University (2024-57).

Twelve-week-old male ($n=16$) and female ($n=32$) C57BL/6J mice were used in this study. The mice were purchased at 3 weeks of age (Japan SLC, Shizuoka, Japan); initially, four same-sex animals were housed per plastic cage (320 mm length × 210 mm width × 130 mm height) and maintained in a regulated environment (24 ± 1 °C; 50 ± 5% relative humidity) with a 12-h light-dark cycle (lights on at 08:00). Food (Oriental MF; Oriental Yeast Co., Tokyo, Japan) and tap water were provided ad libitum. One week prior to the experiments, each animal was housed individually in a small plastic cage (235 mm length × 170 mm width × 120 mm height). This arrangement was adopted for the following reason. Herein, only one mouse was used per experiment; thus, if multiple mice were kept in a single cage, the number of mice would decrease over the course of the experiments, potentially causing stress in the remaining mice. Therefore, to prevent any unexpected effects on the experimental data and ensure animal welfare, we decided to house the mice individually before the experiment.

Rotary motion stimulation

In this experiment, all animals were anesthetized and immobilized to minimize inputs to the inner ear due to body movement. Sixteen female mice were anesthetized with medetomidine hydrochloride (Domitol; Meiji Seika Pharma Co., Ltd., Tokyo, Japan; 0.3 mg/kg, ip), midazolam (Dormicum; Astellas Pharma Inc., Tokyo, Japan; 4.0 mg/kg, ip), and butorphanol (Vetorphale; Meiji Seika Pharma Co., Ltd.; 5.0 mg/kg, ip)[45], followed by additional subcutaneous injection of same volume of these drugs in five parts once every 30 min.

Two hours after the first intraperitoneal drug injection, eight mice were administered an RM stimulus. For RM stimulation, a cage (235 mm length × 170 mm width × 120 mm height) of the same type used for individual housing was fixed to a horizontal rotating platform (425 mm^2), and a paper towel was placed on the bottom. Each deeply anesthetized mouse was carefully placed in the prone position in the cage, with its body axis perpendicular to the diagonal of the platform. The radius from the center of the rotation to the mouse was 125 mm. The mouse was not fixed per se; however, it remained stationary in the cage. The experimenter rotated the platform alternately clockwise and counterclockwise (one rotation every 2 s) for 3 min for a total of 15 min. As controls, eight mice were anesthetized in the prone position without the RM stimulus. All experiments were simultaneously video recorded to ensure that the anesthetized mice remained immobile.

Lowering of barometric pressure

All animals were anesthetized and immobilized in the same manner as described in the "*Rotary motion stimulation*" section. LBP exposure was performed as previously described[41]. Two hours after the first intraperitoneal drug injection, eight male and eight female mice underwent LBP exposure. In the present study, we used a pressure-controlled climatic chamber that could lower the barometric pressure across various rates and ranges[46]. Mice were placed in the chamber at ambient barometric pressure for 120 min (ambient temperature 22 ± 2 °C, relative humidity 50 ± 10%). The barometric pressure in the climate chamber was lowered by 20 hPa from the basal level over 5 min (4 hPa/min) and then immediately returned to the basal level over 5 min (4 hPa/min). The LBP stimulation was repeated three times without a pause. After returning to the basal pressure level following the last repetition, mice were maintained in the chamber for 30 min (Fig. 3). All experiments were simultaneously video recorded to ensure that the anesthetized mice remained immobile.

Eight male and eight female mice placed in the chamber and maintained at ambient pressure without pressure changes for 270 min served as controls. Video recordings were performed concurrently for all experiments to confirm the absence of movement in the anesthetized mice.

The solid black line in the figure indicates the barometric pressure in the climate chamber.

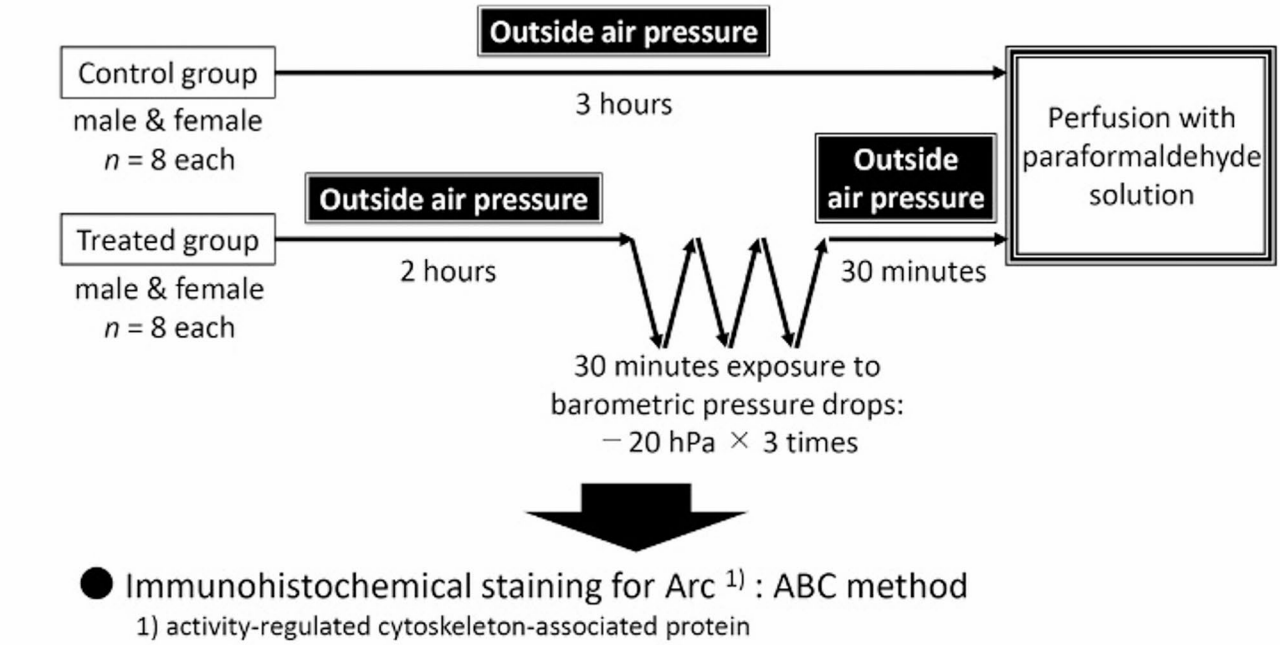

Fig. 3. Protocol for lowering the barometric pressure for immunohistochemical staining for Arc measurements.

Animal treatment and tissue Preparation

One hour after the initiation of the RM stimulation or the LBP exposure, mice were deeply anesthetized with sodium pentobarbital and perfused transcardially with saline, followed by 4% paraformaldehyde in 0.1 M phosphate-buffered saline (PBS; pH 7.4), according to our previous study[11]. Control mice were perfused in the same manner 3 h after the first intraperitoneal anesthetic injection. The mice were then decapitated, decorticated, and post-fixed overnight in the same fixative solution at 4 °C, and then decalcified in a decalcification solution (Decalcifying Soln. B; FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan) for 1 week at room temperature. Decalcified specimens were cut coronally to include the right and left vestibular ganglions and then placed in 30% sucrose in 0.1 M PBS (pH 7.4) for cryoprotection.

Immunocytochemistry for the Arc

Serial coronal Sect. (20 µm thick) were cut from the specimens on a cryostat and mounted on gelatin-coated glass slides. Every two sections containing the vestibular ganglions were used for immunocytochemistry to detect Arc, and the remaining sections were stained with cresyl violet (1% in water). Sections for immunocytochemistry were rinsed with 0.1 M PBS (pH 7.4) and then treated with 3% hydrogen peroxide in PBS for 15 min, according to our previous study[11]. They were then washed with PBS for 20 min, with one buffer change, and rinsed with 0.3% Triton X-100 in 0.1 M PBS (PBST, pH 7.4) for 20 min, with one buffer change; nonspecific binding sites were blocked by incubating the sections in 25% Block Ace (DS Pharma Biomedical, Osaka, Japan) in PBST for 20 min at room temperature. The sections were subsequently incubated with an anti-human Arc antibody (rabbit polyclonal IgG: ARC/ARC3.1 Rabbit Polyclonal antibody; lot number 00094124; Proteintech, Rosemont, IL, USA) diluted 5,000 times with 10% Block Ace in PBST for approximately 40 h at 4°C. After three 10-min washes with PBST, the sections were incubated with a biotinylated anti-rabbit secondary antibody (BA-1000; Vector Laboratories, Burlingame, CA, USA) diluted 500 times with PBST for 2 h at room temperature and then processed with the ABC kit (VECTASTAIN Elite ABC kit PK-6100; Vector Laboratories, Burlingame, CA) appropriately diluted with PBST. Each step was followed by three 10-min washes with PBST. After the last wash, the sections were immersed in 0.175 M sodium acetate buffer (pH 7.4) for 30 min, with two buffer changes, and then appropriately incubated with the chromogen solution (0.02% 3,3'-diaminobenzidine, 0.0025% hydrogen peroxide, and 0.25% nickel (II) chloride hexahydrate in 0.175 M sodium acetate buffer). The reaction was stopped by transferring the sections to a 0.175 M sodium acetate buffer, followed by washing with PBS for 20 min.

Quantification of Arc immunoreactivity and statistical analyses

The total number of Arc-immunoreactive cells in the SVG and IVG was counted bilaterally by an experimenter blinded to the experimental conditions. Each vestibular ganglion was verified using cresyl violet-stained sections adjacent to those used for the observation of Arc-immunoreactive cells.

Data are expressed as mean ± standard error. For the RM stimulation experiments, statistical analyses were performed using the unpaired *t*-test to determine the effect of RM stimulation on the number of Arc-immunoreactive cells in each vestibular ganglion. For the LBP experiments, statistical analyses were performed using two-way analysis of variance followed by a post hoc Tukey–Kramer test to determine the effect of barometric pressure conditions and sex on the number of Arc-immunoreactive cells in each vestibular ganglion. The criterion for statistical significance was set at $p < 0.05$.

Data availability

All data generated or analyzed during this study are shown in the supplementary information file.

Received: 7 August 2025; Accepted: 7 November 2025
Published online: 24 December 2025

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Acknowledgements

This study was supported by a grant from the Chubu University (K). We would like to thank Editage (www.editage.jp) for the English language editing.

Author contributions

J.S. directed the project. J.S. and H.I. wrote the manuscript. H.I. and M.K. performed the in vivo experiments. M.K. and M.Y. performed the immunocytochemistry. T.U. provided project support. J.S. and H.I. performed the data analysis. All the authors approved the manuscript.

Funding

This study was supported by a grant from the Chubu University (K).

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-28093-4.

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