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Electrical Stimulation Can Facilitate Vestibular Compensation Following Unilateral Labyrinthectomy in Rats

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To investigate the effects of electrical stimulation on vestibular compensation, which is the recovery of vestibular symptoms following unilateral labyrinthectomy (UL), intermittent electrical stimulation was applied to the injured vestibular portion in Sprague-Dawley rats. Vestibuloocular and vestibulospinal reflexes, electrical activity and expression of c-Fos protein in medial vestibular nuclei (MVN) were measured with time following UL. Spontaneous nystagmus occurred with frequency of 2.9 ± 0.2 beats/sec at 2 hours after UL and disappeared after 72 hours. Electrical stimulation decreased the frequency of nystagmus significantly till 24 hours after UL. Roll head deviation was $107 \pm 9.7^{\circ}$ at 2 hours after UL and the deviation was maintained till 72 hours, but electrical stimulation decreased the deviation significantly 6 hours after UL. Resting activity of type I neurons in ipsilateral MVN to the injured vestibular side decreased significantly compared with control at 6 and 24 hours after UL, but the activity of type I neurons was recovered to control level by electrical stimulation at 24 hours after UL. Gain of type I neurons induced by sinusoidal rotation of 0.1 Hz decreased significantly till 24 hours after UL, but electrical stimulation restored the activity at 24 hours. The gain of type II neurons decreased significantly at 6 hours after UL, but electrical stimulation restored the activity. Expression of c-Fos protein was asymmetric between bilateral MVN till 24 hours after UL, but the asymmetry disappeared by electrical stimulation 6 hours after UL. These results suggest that electrical stimulation to the injured vestibular portion facilitates vestibular compensation following UL by restoration of symmetry of neuronal activity between bilateral vestibular nuclei resulting from increased activity in ipsilateral vestibular nuclei to the injured side.

Key Words: Vestibular compensation, Vestibuloocular reflex, Vestibulospinal reflex, Neuronal activity, c-Fos protein

INTRODUCTION

Vestibular system located in the inner ear evokes vestibuloocular, vestibulospinal and vestibuloautonomic reflexes by head movement. Peripheral vestibular receptors detect head movement and their afferent signals are transmitted to the vestibular nuclei for inducing vestibular reflexes. Afferent vestibular nerves have a resting activity with 100 spikes/sec at resting position (Goldberg & Fernandez, 1971), which are activated or inhibited by the direction of head movement. Loss of unilateral vestibular function, as a result of unilateral labyrinthectomy (UL), transection of the VIII nerve, or vestibular neuritis, causes an imbalance in resting activity between the bilateral vestibular nuclei, which results in vestibular symptoms including nausea, vomiting, vertigo, spontaneous nystagmus, head oscillation, and head deviation. However, over a period of a few days or weeks following UL, some of these symptoms abate in a process of behavioral recovery known as vestibular compensation (Precht et al, 1966; Smith & Curthoys, 1989). Spontaneous nystagmus resulting from UL

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disappeared within 4 days, but postural disturbance and dynamic symptoms induced by rotation persisted over several months in rabbits and rats (Park et al, 1995, 1997).

Recently, several reports have suggested that the vestibular compensation is attributable to plasticity in the central nervous system, as the vestibular receptors do not regenerate following UL (Jensen, 1983; Park et al, 1995). Considering the main cause of vestibular symptom is deprivation of afferent signals from unilateral vestibular receptors, it is assumed that restoration of the afferent signals from the injured vestibular receptors can recover the vestibular symptoms. If electrical stimulation that is similar to the vestibular afferent signals is applied to the injured vestibular system the vestibular nuclei can restore their activities following UL. Park et al (1995) reported that atypical eye movements induced by sinusoidal rotation and head deviation were restored during electrical stimulation of the injured vestibular system in unilateral labyrinthectomized rabbits. Electrical stimulation of the vestibular system decreased vomiting and nausea in patients with hyperemesis gravidarum (Golaszewski et al, 1995). And increased gastric motility induced by caloric stimulation of the external auditory canal in normal subjects recovered by electrical stimulation of the mastoid process (Park et al, 1999). These reports suggest that electrical stimulation to the injured vestibular system ameliorates acute vestibular symptoms. Repetitive electrical stimulation induced habituation of vestibuloocular reflex (Courjon et al, 1987) and facilitated vestibular compensation (Masumitsu & Sekitani, 1991; Park et al, 1995) in experimental animals, which represent that electrical stimulation may facilitate neuronal plasticity in the vestibular nuclei since the electrical stimulation has a direct effect as well as other metabolic effects (Altman et al, 1979). But the mechanism of electrical stimulation for vestibular compensation was not fully understood.

In order to relieve the acute vestibular symptoms and facilitate vestibular compensation, effects of electrical stimulation to the injured vestibular system on vestibular compensation and the mechanism of electrical stimulation for the compensation were investigated by means of behavioral, electrophysiological, and immunohistochemical studies in unilateral labyrinthectomized rats.

METHODS

Materials

Sprague-Dawley rats weighing 250~300 g with intact vestibular function were used in this study. To select animals with intact vestibular function before labyrinthectomy, vestibuloocular reflex (VOR) induced by sinusoidal rotation of the whole body was assessed. Experimental animals were divided into three groups; control group with intact vestibular function (CON group; n=18), unilateral labyrinthectomy group (UL group; n=36), and UL with electrical stimulation group (UL+ES group; n=24). The procedure used was approved by the Institutional Ethical Committee on Experimental Use of Animals.

Unilateral labyrinthectomy

Under anesthesia with ketamine (40 mg/kg, i.p.), the ventrolateral portion of the neck in supine position was incised to approach the bulla of the external auditory canal. Destruction of the round window and ablation of the ampullary nerve were done under an operating microscope. Left labyrinthectomy, performed in this experiment, was confirmed by the appearance of right-beating nystagmus with eye deviation toward the injured side, and head tilt toward the side of the injured. Gentamicin ointment was applied to the injured ampullary portion, and ampicillin was intramuscularly injected for 3 days.

Electrical stimulation

After labyrinthectomy, in order to apply electrical stimulation to the injured vestibular nerve, a pair of teflon-coated stainless steel wires (0.1 mm in diameter) were implanted in the injured ampullary portion and fixed with dental cement. Electrical stimulation was applied for 12 hours just after UL by 200~300 μA, 1.0 ms, 100 Hz with 5 sec on/off through the electrodes that were connected to the stimulator. Electrical stimulation was applied to free moving animals in cages during day time to reduce stress. In order to evaluate the effects of electrical stimulation on vestibular compensation, eye movement and head deviation were measured 10 minutes after interruption of electrical stimulation.

Recording and analysis of eye movement

A pair of teflon-coated stainless steel wires were implanted chronically in both lateral epicanthi, which were useful to prevent potential changes occurred from changeable electrode locations. Horizontal eye movement was recorded by means of a DC amplifier in the dark during sinusoidal rotation of the whole body about the vertical axis at frequencies of 0.1, 0.2 Hz and maximum velocity of 55°/sec in prone position. In analysing eye movement, the number of spontaneous nystagmus and directional preponderance from slow component velocity of eye movement induced by sinusoidal rotation were calculated. Directional preponderance, which implies a symmetry of the bilateral vestibular functions was calculated by the following formula: (velocity of eye movement in intact side rotation − velocity of eye movement in injured side rotation) ÷ (velocity of eye movement in intact side rotation + velocity of eye movement in injured side rotation) × 100. Decrement of the number of directional preponderance signifies an improvement of a symmetry of the bilateral vestibular functions following UL. In this data 100% of directional preponderance includes more than 100% also, which means left-beating nystagmus was not evoked by leftward rotation.

Head deviation

Head deviation including roll head tilt, yaw head tilt and pitch was measured by motion analyzer. Two video-cameras captured the whole body and it was analyzed in three dimension by personal computer. Roll head tilt was defined as the angle of deviation between a line passing through the center of the animal's head in the coronal plane and gravitational vertical plane.

Electrophyisiological recordings

The animals were anesthetized with ketamine (i.p. 40 mg/kg), secured in a head holder of stereotaxic device (Narishige Co, Japan), and mounted on a servo-controlled rotator, head centered over the axis of rotation with nose 30° down to bring the horizontal semicircular canals close to the horizontal plane of rotation. The body was supported in a horizontal position by a plastic plate hinged to the stereotaxic frame. Artificial respiration was achieved during rotation and body temperature was maintained by heating pad. Action potentials from single neurons were recorded extracellulary using stainless steel microelectrodes with impedence of 4 ~ 8 MΩ. Electrodes were positioned using a micromanipulator into MVN (AP: 11.0 mm, ML: 2.2 mm, DV: 5.8 mm from bregma) according to a stereotaxic atlas (Paxinos & Watson, 1986). Vestibular neurons were classified as type I if their firing rate increased with ipsilateral angular acceleration and decreased with contralateral acceleration (Wilson & Melvill Jones, 1979). Spontaneous activity and activity induced by sinusoidal rotation of the whole body at 0.2 Hz were recorded in MVN at 6, 24 hours following UL. Signals were amplified (CyberAmp 320, USA) and filtered by signal processing system (SPS-8701, Australia) and displayed on an oscilloscope (Tektronix 5113, USA), which were analysed by data analysis program (Spike 2, Cambridge Electronic Design, UK). Gain of neuronal activity obtained from sinusoidal rotation was calculated from maximum neuronal activity divided by maximum stimulus velocity and represented as % change from the gain of control animal.

c-Fos immunohistochemistry

Animals (n=36) were anesthetized with thiopental sodium (IP, 50 mg/kg), prerinsed transcardially with 0.9% saline, and fixed with 4% paraformaldehyde dissolved in a phosphate buffered saline (PBS) solution (pH 7.4) containing 0.05 M Na_2HPO_4, 0.137 M NaCl. The whole brain was then removed, and post-fixed overnight at 4°C. The next day the tissue was blocked and soaked in 30% sucrose at 4°C. The sucrose-embedded brain stem was sectioned at a thickness of 40 μm on a cryostat. Non-specific binding sites were blocked with normal rabbit serum (1 : 50) for 30 min at room temperature. Primary c-Fos antibody (1 : 8000) was applied overnight at 4°C. On the following day the tissue sections were incubated with secondary antibody for 1 hour at room temperature, and then avidin-biotin complex (ABC) for 1 hour at room temperature. The bound complex was visualized by incubating the tissue with 0.05% of diaminobenzidine (DAB) and 0.003% of hydrogen peroxide. After the DAB reaction, the tissue sections were mounted on gelatin-coated slides, dried, dehydrated, and coverslipped. For quantification, c-Fos positive neurons in MVN on both sides were counted using a digital image analysis system.

Statistical analysis

All data were represented as the means±SD. The statistical significance of differences was assessed using analysis of variance (ANOVA). $p<0.05$ was considered significant.

RESULTS

Spontaneous nystagmus

Spontaneous nystagmus (SN) did not appear in the resting position in the absence of any external stimuli in intact labyrinthine rats, but persistent SN was observed following UL. The frequency of SN was 2.9 ±0.2 beats/sec 2 hours after UL and gradually decreased to 1.8±0.5 beats/sec 24 hours after UL, and 0.3±0.2 beats/sec 72 hours after UL. SN disappeared when electrical stimulation was applied to the injured vestibular system following UL, but the nystagmus reoccurred by interruption of the electrical stimulation. However, frequency of SN was significantly decreased by long-term electrical stimulation until 24 hours after UL, and SN disappeared by 72 hours (Fig. 1)

Eye movement induced by sinusoidal rotation

In intact labyrinthine rats, sinusoidal rotation of whole body produced nystagmus, whose direction was consistent with that of sinusoidal rotation and the velocity was symmetrical on both sides. In contrast, only spontaneous nystagmus, the fast component of which was directed toward contralateral to the injured side, occurred immediately after UL regardless of the direction of sinusoidal rotation. In addition, the velocity of nystagmus induced by rotation was faster toward the intact side and slower toward the injured side than that at rest. This abnormal eye movement in response to sinusoidal rotation persisted up to 24 hours at 0.1 Hz and 6 hours at 0.2 Hz rotation. Thereafter, the injured side beating nystagmus was observed by rotation toward the injured side and VOR restored to normal pattern over time. Directional preponderance representing symmetry of bilateral vestibular functions was more than 100% immediately after UL. Moreover, the directional preponderance was 100% until 24 hours at 0.1 Hz of rotation and 6 hours at 0.2 Hz of rotation, which means severe asymmetry of bilateral vestibular functions. The directional preponderance decreased to less than 20% 48 hours after UL at all frequencies of rotation, indicating functional recovery from UL in the

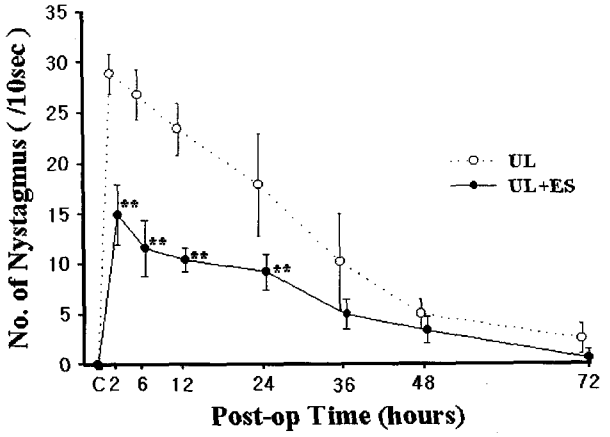

Fig. 1. Effects of electrical stimulation to the lesioned vestibular portion on spontaneous nystagmus following unilateral labyrinthectomy. Number of nystagmus decreased with time. Electrical stimulation was applied to the lesioned vestibular portion for 12 hours with 200~300 μA, 1.0 ms, 100 Hz and 5 sec on/off type. UL, unilateral labyrinthectomy group (n=12); UL+ES, electrical stimulation group (n=12); C, before labyrinthectomy. Values are mean±SD. *significant difference between UL and UL+ES (**$p<0.01$).

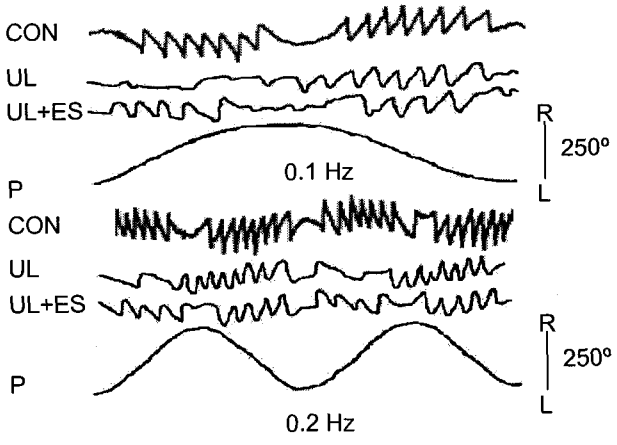

Fig. 2. Restoration of eye movement by electrical stimulation to the lesioned vestibular portion with 200 μA, 1.0 ms, 100 Hz during sinusoidal rotation 6 hours after right unilateral labyrinthectomy. Right beating nystagmus was not induced by rightward rotation of the whole body (UL), but electrical stimulation restored right beating nystagmus during rightward rotation (UL+ES). P, position curve; R, rightward rotation; L, leftward rotation.

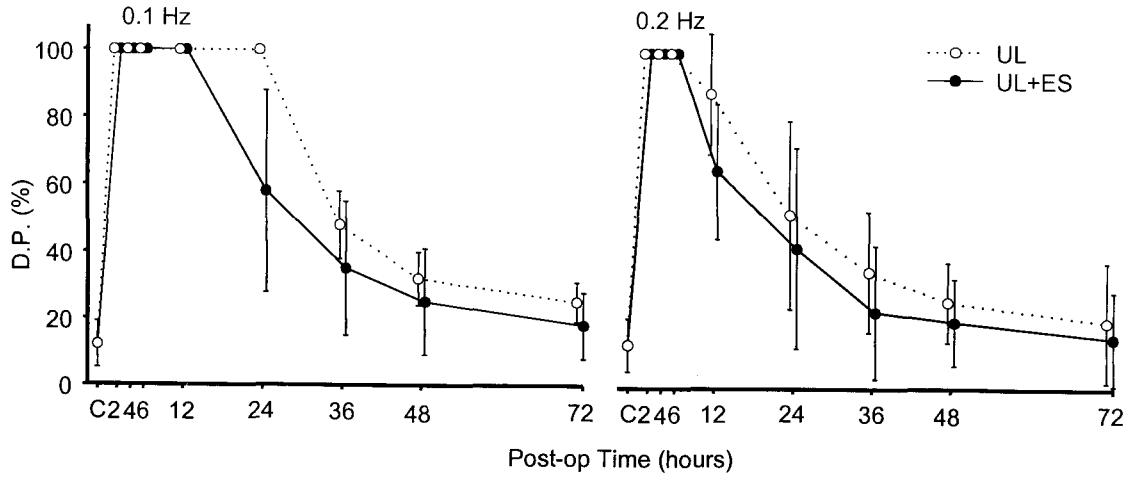

Fig. 3. Directional preponderance (D.P.) of eye movement induced by sinusoidal rotation of the whole body following unilateral labyrinthectomy. 100% includes more than 100%, which represents severe asymmetry between bilateral vestibular function. Notations are the same as in Fig. 1. Values are mean ± SD.

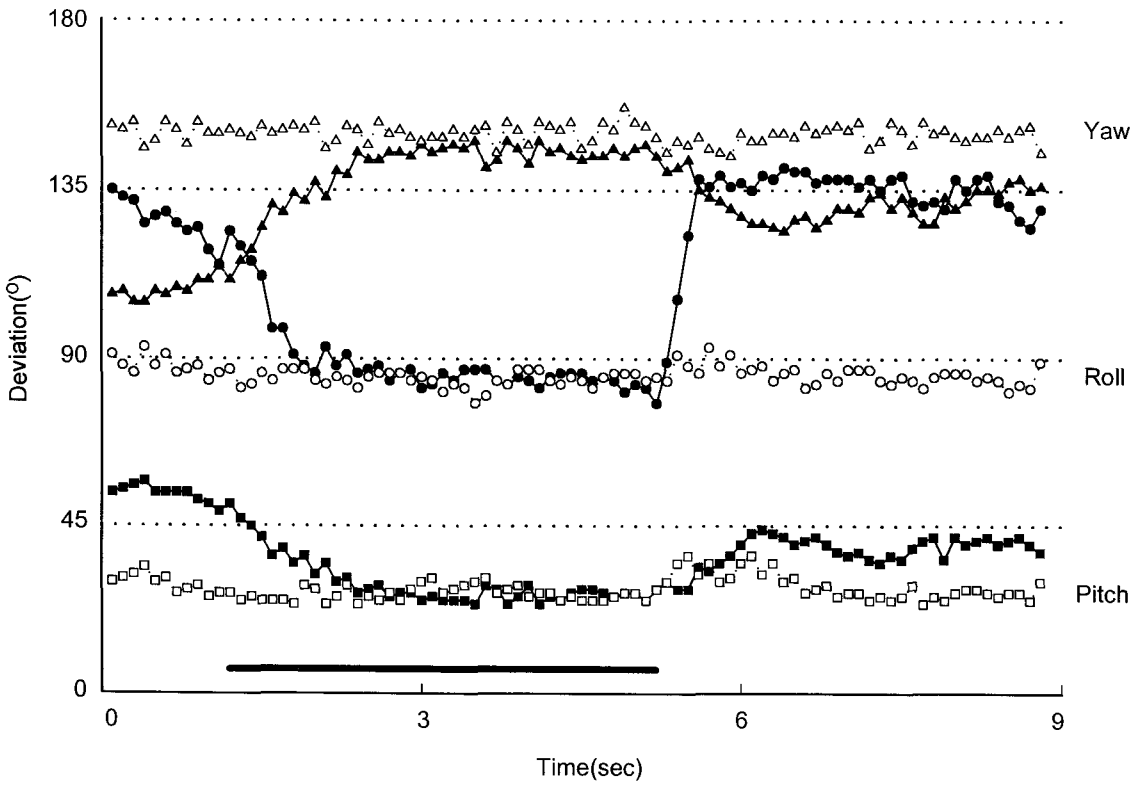

Fig. 4. Dynamic changes of head position during electrical stimulation to the left vestibular system 2 hours after left labyrinthectomy. Yaw, roll, and pitch deviations of head were measured by motion analyzer. Open symbols were obtained from before labyrinthectomy (control) and filled symbols were obtained from left labyrinthectomized rat. Horizontal bar indicates the period of electrical stimulation. Degree of deviation is relative in each plane. Head deviations in all of planes were recovered to control level during electrical stimulation.

injured vestibular system.

Electrical stimulation to the injured vestibular system during sinusoidal rotation following UL restored the normal pattern of vestibuloocular reflex, even on rotation toward the injured vestibular system. However, the direction of eye movement depended on the intensity of electrical stimulation. Long-term electrical stimulation to the lesioned vestibular system facilitated recovery of eye movement induced by sinusoidal rotation following UL. Therefore, recovery of the directional preponderance was also facilitated by electrical stimulation (Figs. 2, 3).

Head deviation

Head and trunk were deviated to the injured vestibular side and rolling movement was occurred immediately after UL. Degree of roll head tilt was 107± 97° at 2 hours after UL and the deviation was maintained till 72 hours after UL. The deviation of head and trunk in roll, pitch and yaw planes disappeared during electrical stimulation to the lesioned vestibular system. However, interruption of electrical stimulation during vestibular compensation elicited reappearance of the head deviation. Long-term electrical stimulation accelerated the decrease of head deviation after UL (Figs. 4, 5).

Electrical activity

In intact labyrinthine rats, the number of resting activity was 18.2±9.0 spikes/sec and 12.6±10.1 spikes/sec in type I and II neurons, respectively. The resting activity of ipsilateral type I neurons to the injured side decreased significantly ($p<0.01$) but the activity of ipsilateral type II neurons increased without significance 6 and 24 hours after UL. Six hours after UL in electrical stimulation group, the resting activity was decreased significantly in ipsilateral type I neurons ($p<0.05$) and increased significantly in ipsilateral type II neurons ($p<0.05$). The resting activity was restored to control level 24 hours after UL (Fig. 6).

Dynamic response of neuronal activity was recorded during sinusoidal rotation at frequency of 0.1 Hz following UL. Gain in ipsilateral type I neurons was decreased up to 38.2±5.9% of control level until 24 hours after UL, but ipsilateral type II neurons showed slightly increased gain compared to control at 6, 24 hours after UL. In electrical stimulation group, the gain of type I neurons was not significantly different from that of control at 24 hours after UL, and the gain of type II neurons did not show significant difference at 6 and 24 hours after UL (Fig. 7).

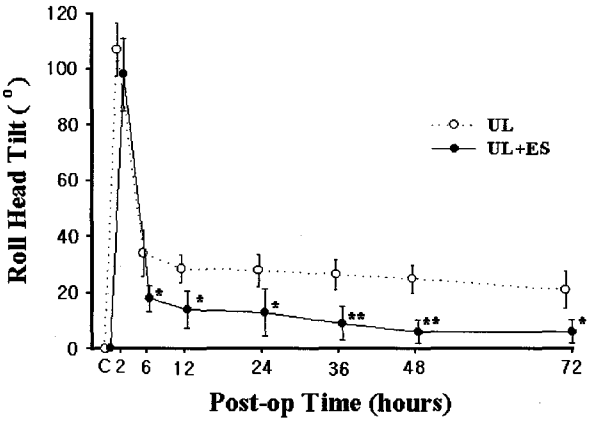

Fig. 5. Effects of electrical stimulation on roll head tilt following unilateral labyrinthectomy. Notations are the same as in Fig. 1. *significant difference between UL and UL+ES (*$p<0.05$, **$p<0.01$).

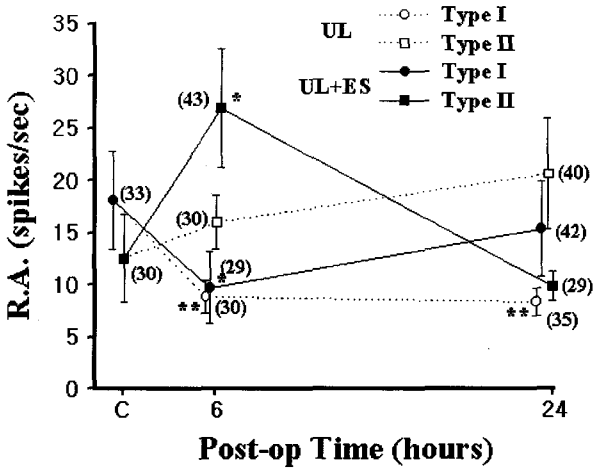

Fig. 6. Changes of resting activity (R.A.) of type I and II neurons in ipsilateral medial vestibular nuclei to the injured vestibular side. Numbers represent number of recorded neurons. *significant difference from control (C) (*$p<0.05$, **$p<0.01$). Notations are the same as in Fig. 1.

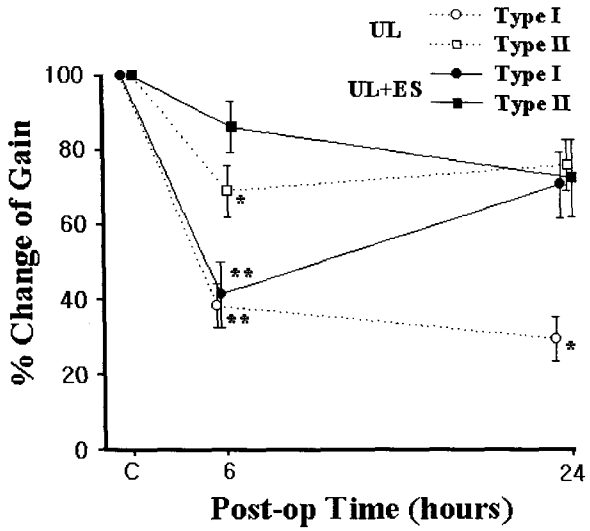

Fig. 7. Dynamic changes of neuronal activity in ipsilateral medial vestibular nuclei to the injured vestibular side induced by sinusoidal rotation of the whole body with 0.2 Hz. Percent change of gain was obtained from the gain of control (C; before labyrinthectomy). The number of recorded neurons is the same as in Fig. 6. Other notations are the same as in previous figures. *significant difference from control (*$p<0.05$, **$p<0.01$).

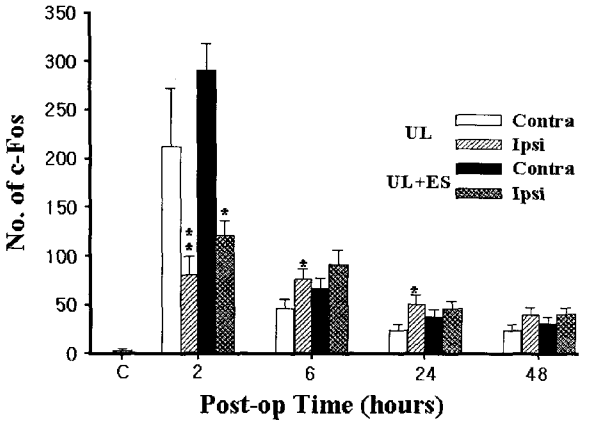

Fig. 8. Changes of c-Fos protein expression in bilateral medial vestibular nuclei following unilateral labyrinthectomy. C, control; Contra, contralateral medial vestibular nuclei to the injured vestibular side; Ipsi, ipsilateral medial vestibular nuclei. Other notations are the same as in previous figures. *significant difference between Ipsi and Contra in each group (*$p<0.05$, **$p<0.01$).

c-Fos protein expression

In rats without UL as a control, few of c-Fos protein was expressed in the brain stem nuclei including medial vestibular nuclei (MVN) and inferior olivary nuclei. Compare to control, UL produced marked expression of c-Fos protein in the bilateral MVN, prepositus hypoglossi, and beta nuclei of inferior olivary nuclei 2 hours after UL. The number of c-Fos protein expression was asymmetrical in bilateral MVN, which showed the induction in contralateral MVN to the injured side was much higher than in ipsilateral MVN ($p<0.01$). Six hours after UL, however, there was a significant reduction of c-Fos protein expression in contralateral MVN than that in ipsilateral MVN so that the number of c-Fos protein expression was slightly higher in ipsilateral MVN than contralateral MVN. Asymmetric c-Fos protein expression between ipsilateral MVN and contralateral MVN was also observed till 24 hours after UL ($p<0.05$) and disappeared 48 hours after UL. The number of c-Fos protein expression in bilateral MVN returned to that of control 120 hours after UL.

In electrical stimulation group, the number of c-Fos protein expression was much higher in contralateral MVN than ipsilateral MVN 2 hours after UL, which was similar to that in UL without electrical stimulation ($p<0.01$). Significant reduction of c-Fos protein expression was observed in contralateral MVN as compared with ipsilateral MVN 6 hours after UL, and the asymmetry of c-Fos protein expression in bilateral MVN disappeared 24 hours after UL. So electrical stimulation to the injured vestibular system facilitated restoration of the symmetry of c-Fos protein expression in the bilateral MVN following UL (Fig. 8).

DISCUSSION

Vestibular symptoms following UL are mainly caused by asymmetry of neuronal activity in bilateral vestibular nuclei which resulted from deprivation of the afferent signals from the injured vestibular receptors (Smith & Curthoys, 1988a, b). VOR induced by sinusoidal rotation just after UL showed that the direction of eye movement was the same as the normal VOR and the velocity was increased by rotation toward the intact labyrinthine side, but the direction was opposite to the normal VOR and the velocity was reduced by rotation toward the injured side. Head was deviated to the injured side following UL. Those abnormal behavioral responses were evoked by relatively high excitation of the intact vestibular system resulting from deprivation of the

afferent signals from the injured vestibular receptors as well as by commissural connection.

Electrical activity of ipsilateral type I neurons to the injured side was decreased just after UL resulting from deprivation of primary afferent signals but the activity of ipsilateral type II neurons was not changed because of commissural inputs through the intact labyrinthine receptors. The activity was asymmetrical in bilateral MVN at the early stage of vestibular compensation and the symmetry was restored with time, which was corresponded with recovery of behavioral response following UL (Smith & Curthoys, 1989; Newlands & Perachio, 1990).

Expression of c-Fos protein, as a useful marker for detecting changes in neuronal activity (Morgan & Curran, 1991), was asymmetrical in bilateral MVN at early stage of vestibular compensation, which was also corresponded with changes of electrical activity. c-Fos protein is expressed within 20 min of depolarization, and marked expression of c-Fos protein in the bilateral MVN 2 hours after UL suggests a synaptic activation from CNS. Especially increase of c-Fos protein expression in ipsilateral MVN to the injured side was resulted from increased intracellular Ca^{++} influx by over-excitation of AMPA/kainate and NMDA receptors (Darlington & Smith, 1996). Asymmetry of neuronal activities between bilateral MVN 2 hours after UL could be explained by more expression of c-Fos protein in contralateral MVN than in ipsilateral MVN. However, remarkable decrease of c-Fos protein in contralateral MVN was due to depression of neuronal activities in contralateral MVN by inhibitory signals from the cerebellum and long-term depression through NMDA receptors in MVN (Kim et al, 1997). Therefore, asymmetry of c-Fos protein expression between bilateral MVN was corresponding to the asymmetry of neuronal activities at the early stage of vestibular compensation.

At the early stage of vestibular compensation, static symptoms after UL including spontaneous nystagmus and head deviation as well as dynamic symptoms including eye movement induced by sinusoidal rotation were abolished by electrical stimulation to the injured vestibular system. However, restoration of behavioral response by electrical stimulation depended on the intensity of electrical stimulation. Higher intensity than optimal stimulation produced the response as if the intact vestibular system was damaged, and lower intensity did not restore the behavioral response (Park et al, 1995).

Considering that vestibular compensation is attributed to restoration of the symmetry of neuronal activity in bilateral vestibular nuclei (Smith & Curthoys, 1989; Newlands & Perachio, 1990; Park et al, 1997), electrical stimulation to the injured vestibular system may useful to restore the symmetry of neuronal activity by substitute for afferent signals in the injured peripheral vestibular receptors (Park et al, 1995, 1999). Several studies suggested that electrical stimulation to the injured vestibular system facilitates the vestibular compensation by activation of ipsilateral vestibular nuclei to the lesion side (Swaak & Oosterveld, 1975; Masumitsu & Sekitani, 1991; Park et al, 1995, 1999). Electrical stimulation to the injured vestibular system activates primary afferent fibers or secondary neurons in the vestibular nuclei, which results in activation of type I vestibular neurons in ipsilateral side to the injury and inhibition of contralateral type I neurons by way of the inhibitory interneuron from the ipsilateral side. The direct effect of electrical stimulation facilitates the restoration of symmetry of the activity between bilateral vestibular nuclei by activation of ipsilateral type I neurons and inhibition of contralateral type I neurons. Facilitated restoration of symmetry in c-Fos protein expression by electrical stimulation may result from afferent signals from the injured peripheral vestibular receptors, however, it is unclear which type of neurons expressed c-Fos protein in this study.

Electrical stimulation is used for therapeutic purposes in the body, such as restoration of motor function or prevention of muscle atrophy following CNS injuries (Graupe & Kohn, 1994; Park et al, 1994). Electrical stimulation has several biological effects including increasing metabolism, blood flow, oxygen consumption (Altman et al, 1979), neuronal plasticity and BDNF production (Mearow, 1998; Kim et al, 2000). On the basis of our results, electrical stimulation may have not only direct effect on the vestibular compensation including substitute for afferent signals from the injured vestibular system but also indirect effect including activation of dormant neural circuit, neuronal sprouting and BDNF production.

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