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Correlation between Electrical Activity of Type I Neuron and c-Fos Expression in the Medial Vestibular Nuclei Following Unilateral Labyrinthectomy in Rats

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To search the correlations between electrical activity and c-Fos expression in the process of vestibular compensation, we examined the changes of those two parameters in the medial vestibular nuclei (MVN) of unilaterally labyrinthectomized (ULX) rats. Spontaneous nystagmus with fast component toward the intact side disappeared gradually within 48 hours. Fourty eight hours after ULX, directional preponderance of the eye movement induced by sinusoidal rotation of the whole body which represents the symmetry of bilateral vestibular functions showed less than 20% by rotation of 0.1, 0.2, and 0.5 Hz, indicating the recovery of symmetry in bilateral vestibular functions. Six hours after ULX, spontaneous electrical activity of type I neurons resulted in asymmetry between bilateral MVN, however, the asymmetry of the electrical activity was decreased 48 hours after ULX. Immunocytochemical staining revealed that ULX produced dramatic induction of c-Fos positive cells in the MVN bilaterally. The number of c-Fos immunoreactive cells in the contralateral MVN was significantly higher than those in the ipsilateral MVN ($p < 0.0001$) 2 hours after ULX. Thereafter, the number of c-Fos positive cells decreased bilaterally and was slightly, but not significantly higher in the ipsilateral MVN at 48 hours after ULX. The present results suggest that both electrical activity of type I neurons and c-Fos expression in MVN following ULX will reflect underlying mechanisms of recovery process of vestibular compensation.

Key Words: Unilateral labyrinthectomy, Medial vestibular nuclei, Vestibular compensation, Eye movement, Electrical activity, c-Fos

INTRODUCTION

Unilateral labyrinthectomy (ULX) caused by Menier's disease, vestibular neuritis, or acoustic tumor results in characteristic symptoms of ocular motor and postural disorders, including spontaneous nystagmus and head deviation. ULX-induced abnomalities of the vestibular function can be divided into two categories on the basis of their relationship to head movement: static symptoms, such as deviation of the eyes and head toward the lesioned side and spontaneous nystagmus which persists in the absence of head movement; dynamic symptoms, such as a reduced amplitude and abnormal timing (gain and phase) of the vestibuloocular (VOR) and vestibulospinal reflexes occurring in response to head movement(Fisch, 1973; Curthoys et al, 1988). As reported by others, some of these symptoms, but not dynamic symptoms diminish in a process of behavioral recovery over a period of time following ULX, known as vestibular

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compensation (Maioli et al, 1983; Igarashi, 1984; Precht, 1986; Smith & Curhtoys, 1989; Kim et al, 1993; Park et al, 1995, 1997).

The symptoms of ULX have been attributed to the loss of resting activity and absence of response to head rotation in neurons in the vestibular nuclei (VN) ipsilateral to lesioned side (Precht et al, 1966). Several lines of evidence suggest that recovery of symptoms is due to the restoration of neuronal activity in the ipsilateral VN, leading to the reestablishment of bilateral symmetry in the resting neuronal activity (Precht et al, 1966; Newlands & Perachio, 1990a, b).

A number of studies have suggested that neuronal plasticity in the central nervous system (CNS) sites, in particular, the ipsilateral VN is responsible for vestibular compensation (Precht et al, 1966; Smith et al, 1986; Smith & Curthoys 1988a, b; Newlands & Perachio 1990a, b; Park et al, 1992). This hypothesis is supported by facts that the vestibular receptors do not regenerate and peripheral neurons in the Scarpa's ganglion do not regain their normal resting activity following ULX (Jensen, 1983). Despite the wide acceptance of the hypothesis that a reduced asymmetry of neuronal activity in the VN mediates recovery process of vestibular symptoms (Galiana et al, 1984; Precht, 1986; Smith & Curthoys, 1988a, b; Newlands & Perachio, 1990a, b), the mechanisms responsible for vestibular compensation remain to be determined.

A variety of stimuli in the CNS are able to induce the expression of c-Fos, one of the immediate early gene products (Dragunow & Faull, 1989; Morgan & Curran, 1991). Recently, c-Fos has been studied to assess changes in neuronal activity in the CNS, including brainstem nuclei following ULX (Kaufman et al, 1992, 1993).

In the present study, to examine the mechanisms accounting for vestibular compensation following ULX, spontaneous nystagmus and eye movement induced by sinusoidal rotation of the whole body were measured in unilaterally labyrinthectomized (ULX) rats. Also, spontaneous activity and dynamic response of type I neurons in the medial vestibular nuclei (MVN) with sinusoidal rotation of the whole body were recorded. Furthermore, the spatial and temporal expression of c-Fos in the MVN following ULX was determined as a process of behavioral recovery. The results presented here will show how electrophysiological and immunohistochemical changes contribute to the recovery process of vestibular symptoms following ULX.

METHODS

Unilateral labyrinthectomy

To make sure of vestibular function intact before labyrinthectomy, vestibuloocular reflex (VOR) induced by sinusoidal rotation of the whole body was assessed in Sprague-Dawley rats weighing 250~300 g. And then, rats were anesthetized with thiopental sodium (IP, 20 mg/kg) and received incision through the ventrolateral portion of the neck in supine position to approach the bulla of the external auditory canal. Destruction of round window and ablation of the ampullary nerve were carried out under an operating microscope. Following left labyrinthectomy, lesion was verified by the appearance of right-beating nystagmus, head tilt towards the side of the lesion, ipsilateral bending of the trunk, and tonic deviation of the eyes.

Recording and analysis of eye movement

A pair of teflon-coated stainless steel wire were implanted chronically in both lateral epicanthi, which was useful to prevent potential changes from changeable location of electrodes. Horizontal eye movement was recorded (n=17) 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, 0.5 Hz in prone position (Park & Park, 1988). In analysing eye movement, the number of nystagmic beats and velocity of eye movement in the slow component of nystagmus were calculated manually. 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 lesioned side rotation) ÷ (velocity of eye movement in intact side rotation + velocity of eye movement in lesioned side rotation) × 100. Decrement of the number of directional preponderance signifies an improvement of a symmetry of the bilateral vestibular functions following ULX. In this data 100% of directional prepondreance includes more than 100% also.

Electrophyisiological recordings

The animals (n=21) were anesthetized with thiopental sodium (IP, 30 mg/kg), secured in a head holder of stereotaxic device (Narishige Co.), 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 for 48 hours following ULX. Signals were amplified and filtered by signal processing system (SPS-8701, Australia) and displayed on an oscilloscope (Tektronix, 5113), which were analysed by data analysis program (Spike 2, Cambridge Electronic Design).

c-Fos immunohistochemistry

Animals (n=18) 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 brainstem 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 diaminobezidine (DAB) and 0.003% of hydogen 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 are represented as the means±SD. The statistical significance of differences was assessed using analysis of variance (ANOVA). $P<0.05$ was conidered significant.

RESULTS

Eye movement

While spontaneous nystagmus did not appear in the resting position without any external stimuli in intact rats, persistent spontaneous nystagmus was observed following ULX. Due to the high velocity of the nystagmus immediately after ULX, the direction of spontaneous nystagmus was defined toward intact side beating at least two hours after ULX. The frequency of spontaneous nystagmus of 3.9±0.5 beats/sec 2 hours after ULX gradually decreased to 0.6±0.2 beats/sec 24 hours after ULX and no nystagmus was

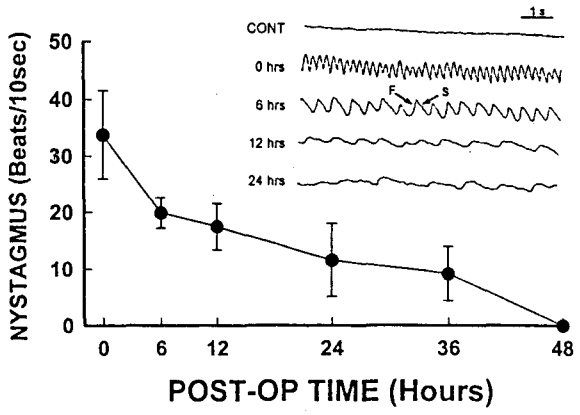

Fig. 1. Recovery of spontaneous nystagmus following left labyrinthectomy. Spontaneous nystagmus disappeared after 48 hours of labyrinthectomy. CONT, control before labyrinthectomy; S & F, slow and fast component, respectively.

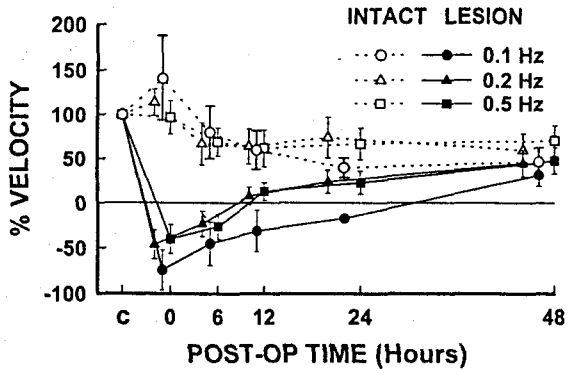

Fig. 2. Percent changes in slow component velocity of vestibuloocular reflex induced by sinusoidal rotation of 0.1, 0.2, 0.5 Hz following left labyrinthectomy. INTACT, rotation toward the intact labyrinthine side; LESION, rotation toward the lesioned labyrinthine side; C, before labyrinthectomy (100%). Negative values are out of phase in eye movement induced by rotation toward the lesioned side.

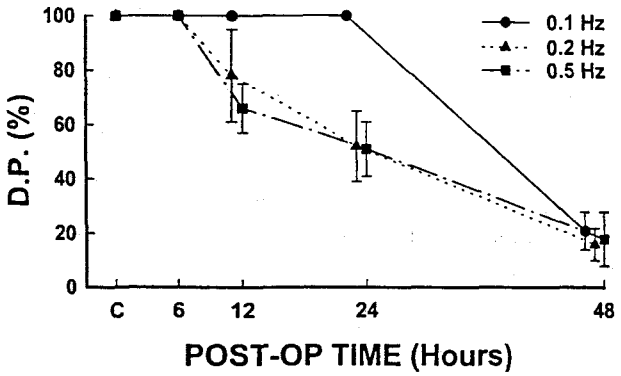

Fig. 3. Directional preponderance (D.P.) of vestibuloocular reflex induced by sinusoidal rotation of 0.1, 0.2, and 0.5 Hz following left labyrinthectomy. D.P. that is more than 100% is also expressed as 100%. D.P. was recovered more rapidly in higher frequency of rotation.

observed 48 hours after ULX (Fig. 1).

In intact rats, sinusoidal rotation of whole body produced nystagmus, whose direction was consistent with that of sinusoidal rotation and velocity was symmetrical on both sides. In contrast, only spontaneous nystagmus, the fast component of which was directed toward contralateral to lesion side, occurred immediately after ULX regardless of the direction of sinusoidal rotation. In addition, the velocity of nystagmus induced by rotation was faster toward the intact side

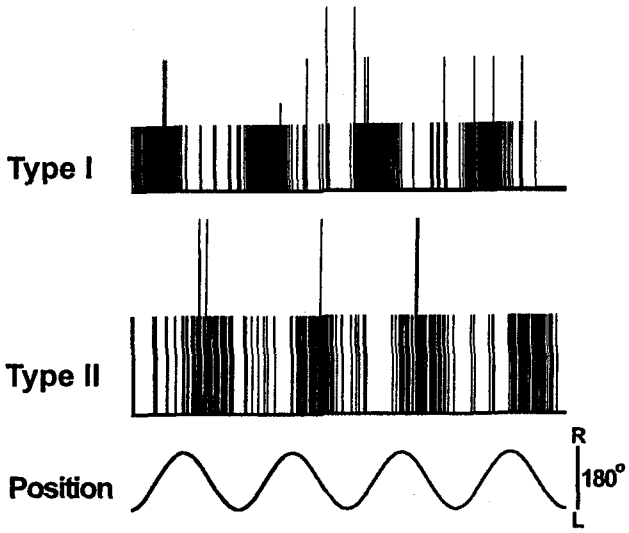

Fig. 4. Electrical activity of type I and type II neurons in the medial vestibular nuclei of intact labyrinthine rat during sinusoidal rotation of 0.2 Hz. Note that acitivity of type I neurons increased by rotation toward recording side and decreased by rotation toward the opposite side, but type II neurons showed opposite response. R & L, rightward and leftward rotation, respectively.

and slower toward lesioned 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, 0.5 Hz rotation. Thereafter, the lesioned side beating nystagmus was observed by rotation toward the lesioned side and VOR restored to normal pattern over time (Fig. 2). Directional preponderance indicative of bilateral vestibular functions was more than 100% immediately after ULX. Moreover, directional preponderance was 100% until 24 hours at 0.1 Hz rotation and 6 hours at 0.2 Hz, 0.5 Hz rotation, which means severe asymmetry of bilateral vestibular functions. And then directional preponderance decreased to less than 20% 48 hours after ULX at all frequencies of rotation, indicating functional recovery from ULX in the lesioned vestibular system (Fig. 3).

Electrical activity of type I neuron in MVN

In rats with intact labyrinth, a wide range of spontaneous discharge of type I neuron was recorded with the resting discharge of 16.7 ± 8.6 spikes/sec. To discriminate between type I and type II neurons in MVN, extracellular recordings were performed during sinusoidal rotation of whole body. The response of type I neurons to sinusoidal rotation depended on the

direction of rotation. Activity of type I neurons increased about two or three folds when the direction of rotation is the same as the recording side and decreased when the direction of rotation is opposite to the recording side. In contrast, activity of type II neurons in response to sinusoidal rotation was opposite to that observed in type I neurons (Shimazu & Precht, 1965) (Fig. 4).

Immediately after ULX, spontaneously active type I neurons in MVN ipsilateral to lesioned side were very few. It was noted that the vestibular symptoms such as spontaneous nystagmus and abnormal VOR persisted even 24 hours after ULX, and the compensation of VOR was accomplished 48 hours after ULX. Based on the above observations, we examined whether behavioral recovery is associated with changes in electrical activity by recording and comparing spontaneous activity of type I neurons 6, 24 and 48 hours after ULX. Six hours after ULX, spontaneous discharge of type I neurons ipsilateral to the lesioned side was 8.6 ± 6.4 spikes/sec, which was attenuated more than 49% compared to that recorded before ULX. In marked contrast with ipsilateral MVN, spontaneous discharge of type I neuron in the contralateral MVN was 13.5 ± 10.0 spikes/sec, indicating more than 19% decrease compared to controls (before ULX). Forty-eight hours after ULX, spontaneous discharge of type I neurons was 12.5 ± 8.4 spikes/sec ipsilaterally and 17.4 ± 8.5 contralaterally. These results show bilateral increases in spontaneous activity in MVN when compared to that recorded 6 hours after ULX, indicating that spontaneous activity of type I neurons in the bilateral MVN approached to normal and subsequently recovered a bilateral symmetry 48 hours after ULX (Fig. 5). In addition, dynamic response of type I neurons induced by sinusoidal rotation in the lesioned MVN recovered with time (Fig. 6).

c-Fos expression in MVN following ULX

c-Fos positive cells were hardly seen in MVN of intact rats. c-Fos immunoreactivity was found only in a few cells in the reticular formation and periaquaductal gray area of the brainstem. After ULX, however, a dramatic increase in c-Fos expression was noticed in MVN bilaterally. In unilaterally labyrinthectomized rats, the number of c-Fos positive cells were 212 ± 60 in the intact MVN and 81 ± 19 in the lesioned MVN

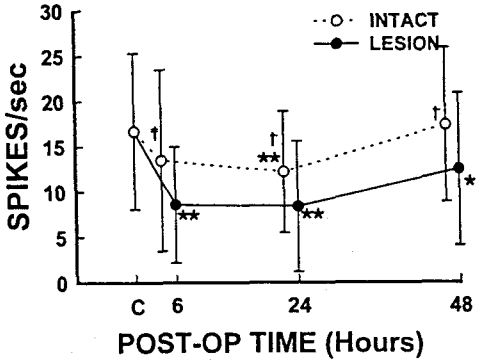

Fig. 5. Spontaneous activity of type I neurons in the medial vestibular nuclei (MVN) following unilateral labyrinthectomy (ULX). The activity was decreased following ULX in the bilateral MVN and the lesioned side decreased more prominent. The activity recovered gradually after 48 hours of ULX. INTACT, MVN contralateral to ULX; LESION, MVN ipsilateral to ULX; C, control before ULX. *$p<0.05$, **$p<0.01$, compared with control. $^{\dagger}p<0.05$, $^{\dagger}p<0.01$, compared with lesioned side.

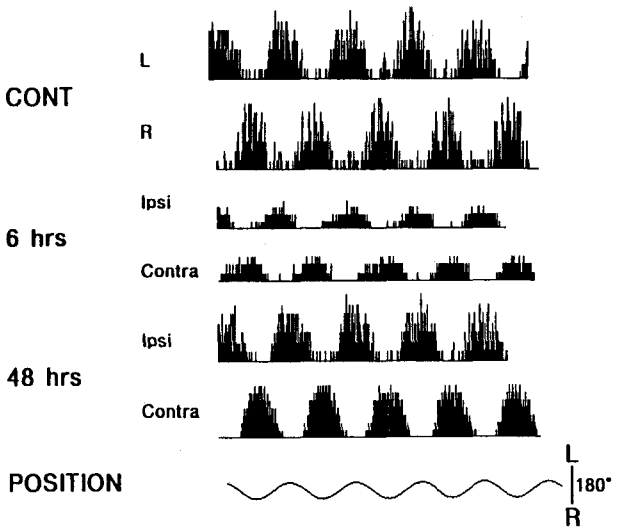

Fig. 6. Dynamic response of type I neurons induced by sinusoidal rotation of 0.2 Hz in bilateral MVN following ULX. The activities were decreased in bilateral MVN 6 hours after ULX, but they were recovered 48 hours after ULX. The recovery of dynamic response was similar to that of spontaneous activity. CONT, control before ULX; L, left MVN; R, right MVN; Ipsi, ipsilateral to lesion (left); Contra, contralateral to lesion (right).

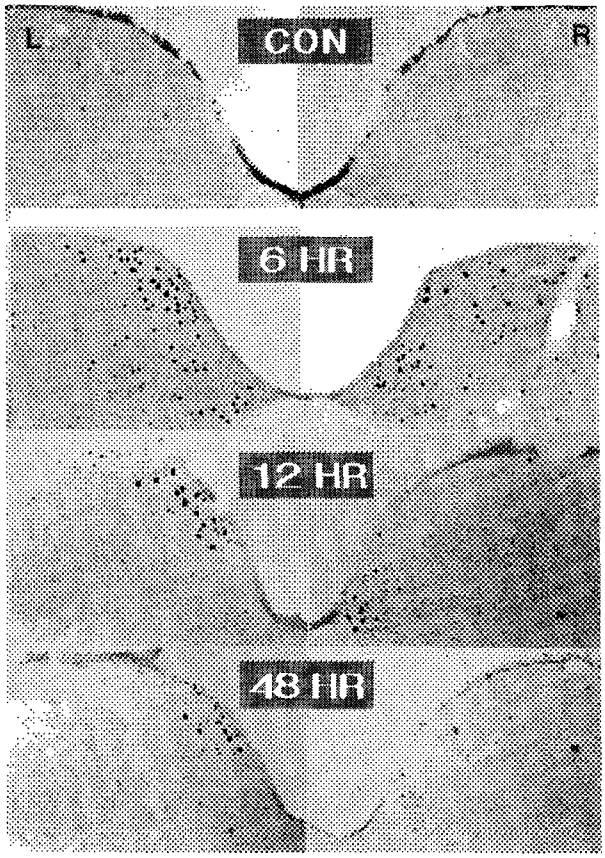

Fig. 7. Photomicrographs of c-Fos immunoreactive cells in MVN following left ULX. c-Fos was not expressed in control group (CON), whereas a large number of c-Fos immunoreactive cells were expressed in MVN ipsilateral to ULX at 6 hours after ULX. A small number of immunoreactive cells were also expressed in the prepositus hypoglossal nuclei. c-Fos immunoreactive cells disappeared after 48 hours of ULX. Time represents hours after post-labyrinthectomy.

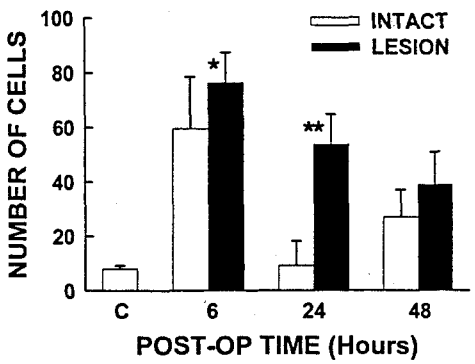

Fig. 8. Number of c-Fos immunoreactive cells in MVN following ULX. INTACT, MVN contralateral to ULX; LESION, MVN ipsilateral to ULX. *$p<0.05$, **$p<0.01$, compared with intact side.

two hours after ULX, demonstrating severe asymmetry of the number of c-Fos immunoreactive cells ($p<0.0001$). While overall number of c-Fos positive cells was lower, there was still a significant difference ($p<0.05$) in c-Fos positive cell number between MVN on left and right sides 6 ($p<0.05$), 24 ($p<0.01$) hours after ULX. Interestingly, higher expression of c-Fos occurred in the ipsilateral MVN than that seen in the contralateral MVN after 6 hours of labyrinthectomy. After functional recovery from the vestibular symptoms 48 hours after ULX, no difference in c-Fos expression was found. Seventy-two hours after ULX, only a few c-Fos positive cells were detected in MVN (Figs. 7, 8).

DISCUSSION

The vestibular system is widely spread in the CNS and receives afferent signals from the vestibular receptors, cerebellum and brainstem. Since there is no evidence for the regeneration of vestibular receptors and Scarpa's ganglion following labyrinthectomy (Jensen, 1983) it is hypothesized that vestibular nuclei may play an important role for vestibular compensation. The results of the present study demonstrate that disappearance of spontaneous nystagmus and recovery of eye movement induced by rotation following ULX are accomplished when spontaneous activity of type I neurons restores a symmetry in the bilateral MVN. Moreover, behavioral recovery is accompanied by changes in c-Fos expression induced by ULX. Spontaneous nystagmus occurring immediately after ULX was very fast and persistent, the fast component of which was directed toward the intact side. Spontaneous nystagmus decreased gradually over time and disappeared within 48 hours after ULX. Disappearance of spontaneous nystagmus observed in the present study was somewhat faster compared to that reported by others (Precht et al, 1966; Maioli et al, 1983; Sirkin et al, 1984). It is likely that ULX gives rise to an excitatory effect on the contralateral vestibular system and an inhibitory effect on the ipsilateral one. This elicits the contraction of superior

rectus, superior oblique, medial rectus on the contralateral eye, and the contraction of inferior rectus, inferior oblique, lateral rectus on the ipsilateral eye (Kim et al, 1987). Therefore, the direction of spontaneous nystagmus following ULX probably resulted from the correlation between vestibular semicircular canals and extraocular muscles.

The present results also indicate that direction and velocity of eye movement induced by sinusoidal rotation immediately after ULX dissociate from the direction of rotation compared to that observed from nomal VOR. The complete suppression of the lesioned vestibular system immediately after ULX may account for difference in eye movement. However, the restoration of eye movement to normal pattern was achieved by 6 hours at a frequency of 0.2 Hz and 0.5 Hz, and by 24 hours at a frequency of 0.1 Hz, respectively. In addition, 48 hours after ULX, directional preponderance of VOR was less than 20% at three different frequencies. This compensatory process over the course of time is possibly due to disinhibition of the vestibular system contralateral to lesioned side and enhancement of a suppression from intact vestibular system through commissural pathways following ULX (Precht et al, 1966; McCabe et al, 1972; Ried et al, 1984; Smith & Curthoys, 1988a, b). Considering that the vestibular receptors do not regenerate following ULX (Jensen, 1983), the recovery of VOR in the present study could also imply that the spontaneous activity of vestibular nuclei increased on the lesioned side and was suppressed on the intact side over time after ULX.

The spontaneous discharge rate of type I neuron was lower in guinea pig (Smith & Curthoys, 1988a, b), but higher in gerbil (Newlands & Perachio, 1990a, b) than that in rat with the intact labyrinth. These discrepancies may result from species difference as well as degree of anesthesia and recording methods used in the present study. A three-fold increase in spontaneous activity was obtained by sinusoidal rotation toward recording side, while rotation toward opposite direction masked neuronal activity, demonstrating the typical features of type I neurons in the vestibular nuclei.

Active type I neurons were barely found in the lesioned MVN due to the deprivation of afferent signals immediately after ULX. Twenty-four hours after ULX, a wide range of spontaneous discharge rate prevented experimental groups from showing a statistical significance although recovery of spontaneous activity occurred bilaterally. Accompanying behavioral recovery 48 hours after ULX, there was a decreased bilateral asymmetry of the spontaneous activity of type I neurons. However, the neuronal activity in the lesioned side did not reach control value (before ULX), and the intact side had higher activity. The present results are comparable to other studies. Newlands and Perachio (1990a, b) reported that four to seven weeks after ULX, the spontaneous activity of type I neurons is higher in contralateral side and lower in ipsilateral side compared to that before ULX. Whereas, the completely opposite direction for recovery pattern of type I neurons has been shown (Smith & Curthoys, 1988a, b). These studies demonstrated that 60 hours after ULX, the lesioned side has higher neuronal activity than the intact side. Moreover, neuronal activity in the lesioned side is 30% higher compared to control (before ULX). These results are contradictory to the finding that the neuronal avtivity in the lesioned side would never be higher than that in the intact side with even longer intervals for recovery after ULX (Schaefer & Meyer, 1974). It is likely that these inconsistencies may be, in part, due to species difference as well as different intervals for recovery after ULX.

Our immunohistochemical study showed that c-Fos was expressed in MVN 2 hours after ULX and this was more pronounced in the intact side. There are several explanations for the c-Fos expression, including the expansion of peripheral innervation, unmasking of existing connections (Mendell, 1984), functioning blind axonal endings (Snow & Wilson, 1990), supersensitivity and up-regualtion of receptors for neurotransmitters. In addition, the neuronal activation caused by mechanical stimulation of the vestibular system during labyrinthectomy cannot be excluded because of an immediate response of c-Fos expression (Hunt et al, 1987; Bao et al, 1993). The relatively lower expression of c-Fos in the lesioned side might be due to deprivation of afferent signals from the lesioned vestibular system. Alternatively, it might be due to that the neurons expressing c-Fos are not type I. In line with this idea, we noticed that c-Fos expression detected 2 hours after ULX did not correspond to electrical activity of type I neurons in bilateral MVN.

The observation that MVN on the lesioned side had higher c-Fos expression than the intact side 6

hours after ULX is interesting. In a previous study the spatial pattern of c-Fos expression was shown to be reversed by the treatment with MK801, an NMDA receptor antagonist (Kim et al, 1997). In this study, similar to the behavioral recovery, c-Fos expression in the MVN was symmetrical 48 hours after ULX and reduced to nondetectable levels 72 hours after ULX. These changes in c-Fos expression might be regulated by complicated anatomical pathways, including the commissural connections (Precht et al, 1966), and inputs from the cerebellum (Kitahara et al, 1995) and the brain stem. A variety of neurotransmitters existed in the vestibular system may also take part in long-term changes in c-Fos expression. These interpretations would support the persistence of c-Fos expression for more than 48 hours after ULX because half-life of c-Fos protein is about 24 hours (Dragunow & Faull, 1989; Morgan & Curran, 1991; Kaufman et al, 1993).

In summerizing, the present results demonstrate that functional recovery from ULX was associated with corresponding changes in electrical activities of type I neurons in MVN and concurrent expression of c-Fos protein in unidentified MVN neurons. We suggest that these changes might underlie the recovery process of vestibular compensation.

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