Investigation of Central Mechanisms underlying Compensation in the Hemilabyrinthectomized Cat

Minoru MAEDA, Makoto MIYAOKA* and Shozo ISHII**

Department of Neurosurgery and Casualty Center, Juntendo University
Izunagaoka Hospital, Shizuoka;
*Department of Neurosurgery, Fujisawa City Hospital, Fujisawa, Kanagawa;
**Department of Neurosurgery, Juntendo University School of Medicine, Tokyo

Abstract

The autoradiographic [14C]deoxyglucose method for quantitative determination of local cerebral glucose utilization (LCGU) was used to study the compensatory process following hemilabyrinthectomy in adult cats. In the critical stage when the cats were uncompensated, LCGU in the deafferented vestibular nuclei was well below that of the intact side. Increased LCGU was seen in contralateral nucleus reticularis parvocellularis, the bilateral nuclei pontis, and the ipsilateral abducens nucleus and its ventral parts. Activity levels in the inferior olive were essentially unchanged. In the cerebellum, the posterior vermis and the nodulofloccular lobe were very active. LCGU in the cerebellar nuclei was not noticeably changed. In the compensatory stage, the rate of LCGU in the deafferented vestibular nuclei had increased to that of the intact side. The increased LCGU was bilaterally evident in the nuclei reticularis parvocellularis, gigantocellularis, and lateralis, and superior colliculus. The posterior vermis, nodulus, and cerebellar nuclei were active.

Destruction of the vermis, fastigial nuclei, and surrounding white matter produced marked imbalance during walking and a tremor of the head during feeding. These signs subsided very gradually. Interruption of the transreticular vestibular crossed connection produced severe motor disturbances on standing, walking, and feeding, and normal function was not restored. These findings suggest that vestibular compensation results from the combined activity of many brainstem and cerebellar structures, where intervestibular crossed pathways are considered an important factor in compensation.

Key words: vestibular compensation, [14C]deoxyglucose, hemilabyrinthectomy, brainstem, cerebellum, vestibular crossed connection

Introduction

In men and animals, hemilabyrinthectomy produces a characteristic behavioral pattern. Functional recovery following unilateral destruction occurs rapidly and is remarkably complete. This compensatory process, which is basically similar in all vertebrates, has been well recognized since the early investigations of Bechterew2) and Ewald7) in the late 1800s. In these studies this process occurred in three distinct stages differentiated by their characteristic behavioral patterns. In the critical stage, beginning immediately after hemilabyrinthectomy, the animals exhibit severe symptoms of imbalance, including rapid, spontaneous nystagmus, severe head deviation, and circling or rolling toward the deafferented side. The acute stage is marked by a rapid partial recovery of asymmetry. Restoration of normal functioning occurs during the compensatory stage.

In cats, lesion-induced symptoms of ocular and postural imbalance recover almost to control values within the first postoperative week. Essentially similar results have been obtained in other species, although the time courses of recovery vary considerably. It takes only hours for compensation of head tilt in the rat. Ocular imbalance abates within a similar period of time in rats, guinea pigs, and cats.

According to electrophysiological investigations of the vestibular nuclei of the cat, the most salient characteristics are a decrease in spontaneous activity in the deafferented vestibular nuclei, which begins...
immediately after unilateral labyrinthectomy and lasts for several days, and restoration of normal activity in the compensatory stage. Although changes in the activity of neurons within the deafferented vestibular nuclei may play a role in compensation, structures other than the vestibular nuclei most often found to play a role in rapid and complete compensation are the spinal cord, the cerebellum, the cerebellar nuclei, and the visual system. Concerning the role of the cerebellar system in vestibular compensation, Llinas and Walton concluded that the cerebellar nuclei and the integrity of the inferior olive are important in achieving and maintaining compensation. Most recently, Galiana et al. showed that commissural pathways, which connect the two sides of the brainstem, are possibly important sites of adaptive modulation of the static characteristics of vestibular responses.

To examine this area further, we performed two sets of experiments. In the first we used the autoradiographic \([^{14}C] \text{deoxyglucose} \) method for quantitative determination of local cerebral glucose utilization (LCGU) and served as a marker for the plastic changes generating vestibular compensation. Our second object was to elucidate the effects of interruption of crossed vestibular nuclear coupling via transreticular and transcerebellar pathways on vestibular compensation, using chronically hemilabyrinthectomized cats. We shall first describe the changes that occurred in the various nuclei of the brainstem and the cerebellum and then discuss the importance of vestibular crossed pathways involving both the brainstem and the cerebellum. Some of the results we present have appeared in brief form and were presented at the Satellite Symposium on Vestibulospinal Control of Posture and Movement in Bologna in 1987.

Materials and Methods

Labyrinthectomy was performed in halothane-anesthetized cats by the ventral extracranial approach. Two hours, 24 hours, 4 weeks, and 10 months after hemilabyrinthectomy, LCGU was measured, with the cats sitting in partial restraining bags.

I. Autoradiographic \([^{14}C] \text{deoxyglucose} \) method

An intravenous pulse of \(2-[^{14}C] \text{deoxyglucose} \) (125 \(\mu \text{Ci/kg} \)) was administered, and its plasma concentration as well as that of glucose were subsequently monitored. The animals were sacrificed after 45 minutes and their brains were dissected, frozen in Freon 12, mounted in embedding medium, and sectioned into 20-\(\mu\)m slices with a cryostat. The autoradiographically determined \([^{14}C] \) concentrations were densitometrically measured. The optical density values, plasma variables, and kinetic constant were used to calculate the rates of LCGU, according to the equation described by Sokoloff et al. LCGU was compared in normal, uncompensated, and compensated animals.

II. Lesions in the cerebellum and brainstem

The behaviors of four hemilabyrinthectomized cats that had fully recovered were observed. The posterior vermis, fastigial nuclei, and surrounding white matter were aspirated by suction via suboccipital craniectomy. In six other cats the vermis, fastigial nuclei, and surrounding white matter were removed, exposing the fourth ventricle. The brainstem was cut longitudinally along the midline from the caudal end of the inferior colliculus to the obex, obliterating neural interactions between the bilateral vestibular nuclei through the brainstem. The longitudinal incision was not extended to the ventral surface of the brainstem but to a depth of 4.0–5.0 mm from its dorsal surface along the midline. The extent of the lesion in the cerebellum and the brainstem was determined histologically by means of Klüver-Barrera-stained serial sections. For further documentation of our observations, the animals were filmed at various points during the study.

Results

Postural characteristics of the cats 2 hours following right hemilabyrinthectomy are shown in Fig. 1A. The animals were very unstable and tended to circle toward the lesioned side. In the critical stage rapid, spontaneous vestibular nystagmus of 80 to 120 beats per minute was observed. By 24 hours following hemilabyrinthectomy, the rate had slowed remarkably, to 30 to 50 beats per minute. Figure 1C and D illustrates the time course of vestibular compensation in the cat. Within 2 to 3 weeks after hemilabyrinthectomy, the above mentioned postural abnormalities had almost completely disappeared (Fig. 1B) except when the animals were under light anesthesia.

I. Normal cats

Autoradiographs of selected regions of the brainstem and cerebellum of a normal, conscious cat are illustrated in Fig. 2. A coronal section taken through the cerebellar cortex revealed that the radioactivity was concentrated in the granular and Purkinje cell layers. In this figure the cerebellar...
nuclei can be seen very clearly and the fastigial, interpositus, and dentate nuclei can also be distinguished. Within the brainstem several cell groups are recognizable: the vestibular nuclei, inferior olive, and colliculus. The rates of LCGU were measured in the following structures of the brainstem: vestibular nuclei (medial, lateral, and inferior), nuclei reticularis parvocellularis, gigantocellularis, and lateralis, formatio reticularis, inferior olive, abducens nucleus and its vicinity, superior colliculus, and nucleus reticularis pontis. In the cerebellum the LCGU rates were measured in the anterior and posterior vermis, hemisphere, nodulofloccular lobe, and cerebellar nuclei (fastigial, interpositus, and dentate).

The rates of LCGU in the brainstem and cerebellum of conscious cats are listed in Table 1. The rates in gray matter were much higher than those in white matter. The values for LCGU in the conscious cat were considerably lower than those observed in the conscious rat.\(^{29,30}\) The highest rate was in the inferior colliculus, as has also been reported in the rat and the monkey.\(^{29,30}\)

**II. Uncompensated cats**

Two hours after right hemilabyrinthectomy, during the critical stage when the cats were uncompensated, distribution of activity within the brainstem and cerebellum was significantly different from that in the normal cat. Figure 3 shows the relative rates of LCGU in the lesioned cats (2 hours after right hemilabyrinthectomy), compared with normal control values. The greatest difference was in the medial, lateral, and inferior vestibular nuclei, where LCGU in the deafferented nuclei was well below (62% of the control value) that of the intact side (101% of the control value). Increased LCGU rates were noted in the contralateral nucleus reticularis parvocellularis (125%), bilateral nuclei pontis (150%), the ipsilateral abducens nucleus and its ventral parts (as high as 212%), and the ipsilateral superior col-
In the contralateral superior colliculus the LCGU rate was reduced to 73%. Activity levels in the inferior olive changed little during the critical stage (102% of the control value). In the cerebellum, the posterior vermis and the nodulofloccular lobe were very active. The LCGU rate in the cerebellar nuclei was fairly normal.

The rates of LCGU at 24 hours after right hemilabyrinthectomy were very similar to those at 2 hours after operation. Decreased activity was observed in the deafferented vestibular nuclei, while the LCGU rate was bilaterally increased in the nuclei reticularis parvocellularis, formatio reticularis mesencephali, and nuclei pontis. The inferior olive was also slightly active. In the cerebellum, the posterior vermis and nodulofloccular lobe were also active (Fig. 4).

### Table 1 LCGU in the brainstem and cerebellum of conscious cats, rats, and monkeys (μmol/100 gm/min)

<table>
<thead>
<tr>
<th>Structures</th>
<th>Cat (control)</th>
<th>Rat*</th>
<th>Monkey**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brainstem:</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Vestibular nuclei:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial</td>
<td>56.7</td>
<td>66</td>
<td>3</td>
</tr>
<tr>
<td>Lateral</td>
<td>52.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>47.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleus reticularis parvocellularis</td>
<td>24.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleus reticularis gigantocellularis</td>
<td>28.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleus reticularis lateralis</td>
<td>27.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formatio reticularis</td>
<td>21.5</td>
<td></td>
<td></td>
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<tr>
<td>Inferior olive</td>
<td>70.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdusens nucleus and its ventral parts</td>
<td>21.5</td>
<td></td>
<td></td>
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<tr>
<td>Inferior colliculus</td>
<td>118</td>
<td>197</td>
<td>103</td>
</tr>
<tr>
<td>Superior colliculus:</td>
<td></td>
<td>95</td>
<td>55</td>
</tr>
<tr>
<td>Superficial layer</td>
<td>55.5</td>
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<tr>
<td>Intermediate and deep</td>
<td>42.6</td>
<td></td>
<td></td>
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<td>Formatio reticularis mesencephali</td>
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<tr>
<td>Nucleus reticularis pontis</td>
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<td>Nucleus pontis</td>
<td>32.0</td>
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<tr>
<td><strong>Cerebellar cortex:</strong></td>
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<td>57</td>
<td>31</td>
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<tr>
<td>Anterior lobe:</td>
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</tr>
<tr>
<td>Vermis</td>
<td>39.7</td>
<td>37.2</td>
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<tr>
<td>Paramedian</td>
<td>44.8</td>
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<td>Posterior lobe:</td>
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</tr>
<tr>
<td>Uvula</td>
<td>45.7</td>
<td>37.2</td>
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<td>Pyramid, Tuber</td>
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<tr>
<td>Hemisphere</td>
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<tr>
<td>Nodulofloccular lobe:</td>
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<tr>
<td>Nodulus</td>
<td>50.5</td>
<td>45</td>
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<tr>
<td>Flocculus</td>
<td>61.5</td>
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<td>Cerebellar nuclei:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fastigial</td>
<td>100</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Interpositus</td>
<td>43.7</td>
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<td>12</td>
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<tr>
<td>Dentate</td>
<td>45.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White matter</td>
<td>12.3</td>
<td>37</td>
<td>12</td>
</tr>
</tbody>
</table>

*Data from Sokoloff et al., 1977.** Data from Sokoloff, 1978.

### III. Compensated cats

Four weeks after right hemilabyrinthectomy, in the compensatory stage, the most salient feature was that the rate of LCGU in the deafferented vestibular nuclei (85–95%) had increased to equal that of the intact side (95%). Moderately increased activity was seen in the bilateral nuclei reticularis parvocellularis. On the other hand, the LCGU rate in the inferior olive was almost equal to that of the control cat (101–111%). In the cerebellum, the posterior vermis was very active (as high as 160%), and increased LCGU was also observed in the fastigial, interposi-
tus, and dentate nuclei (Fig. 5 upper).

Ten months after right hemilabyrinthectomy, when the cats were completely compensated, the rates of LCGU were very similar to those at 4 weeks. No asymmetry was observed in the bilateral vestibular nuclei. The LCGU was bilaterally increased in the nuclei reticularis parvocellularis (140% of control), gigantocellularis (115%), and lateralis (157–
Compensation after Hemilabyrinthectomy

Fig. 5  Percentage change in LCGU in compensated cat, 4 weeks (upper) and 10 months (lower) following right hemilabyrinthectomy, compared with normal control values.

Fig. 6  Percentage change in LCGU in the cat (accompanied by Bechterew's phenomenon \(^2\)), compared with normal control values. During the compensatory stage, 3 months after right hemilabyrinthectomy, the left labyrinth was destroyed. LCGU was measured 2 hours after the second (left) labyrinthectomy.

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167%), and superior colliculus (130%). The posterior vermis (160%), nodulus (179%), and cerebellar nuclei (fastigial 150%, interpositus 130%, dentate 130%) were active as well (Fig. 5 lower).

In the completely compensated cat (3 months after right hemilabyrinthectomy), destruction of the contralateral (left) labyrinth produced a distinct nystagmus, its quick component being directed toward the first operated labyrinth, as if it were still intact. This phenomenon is called Bechterew's compensatory nystagmus. The second labyrinthine destruction was also accompanied by head rotation and ocular deviation, as if the first labyrinth were still intact. Two hours after the second (left) labyrinthectomy, the rates of LCGU were quite similar to those of the previously described 2-hour postoperative (uncompensated) cat. LCGU in the left vestibular nuclei (the second labyrinthectomy side), at 66 to 86% of the control value, was well below that of the first deafferented vestibular nuclei (80-100%). Increased activity was bilaterally noted in the nuclei reticularis parvocellularis and lateralis, formatio reticularis, nuclei pontis, posterior vermis, and nodulofloccular lobe (Fig. 6).

IV. Effect of cerebellar lesions

Destruction of the vermis, bilateral fastigial nuclei, and surrounding white matter in four animals subjected to hemilabyrinthectomy 1, 2, or 3 months previously and fully compensated produced marked imbalance during walking and a tremor of the head during feeding. These signs subsided very gradually.

V. Effect of interruption of vestibular crossed pathways

Destruction of the transreticular and transcerebellar crossed connections between bilateral vestibular nuclei (Fig. 7A and B) in six animals hemilabyrinthectomized 2 to 6 months previously and fully compensated (Fig. 7C) produced tilting of the head toward the hemilabyrinthectomized side (Fig. 7D). These animals showed severe motor disturbance during standing, walking, and feeding and in fact were almost unable to stand and walk. A very pronounced head tremor was observed in all animals. This tremor subsided when the animals were at rest, but was always present during feeding. The severe motor disturbance did not abate during the 2- to 4-month observation period.

Discussion

Rates of LCGU in the cat vary over a wide range, as in the rat. The rates in gray matter were generally three to five times those in white matter. In the conscious cat, LCGU was considerably lower than that observed in the conscious rat, and was very similar to that in the monkey. In the critical stage, 2 hours after hemilabyrinthectomy, LCGU in the deafferented vestibular nuclei (62%) was well below that of the intact side. This is consistent with electrophysiological findings of decreased spontaneous activity in the critical stages following peripheral vestibular lesioning. Increased activity was seen in the nucleus reticularis parvocellularis, the ventral part of the abducens nucleus, the posterior vermis, and the nodulofloccular lobe. These local changes in the LCGU rates may have been related to the generation of vestibular nystagmus and the marked postural abnormalities, and they may also have contributed to initiation of the compensation process. LCGU in the flocculus was very high (121 μmol, or 197% of the control.

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value) in the uncompensated stage and was not markedly increased in the compensatory stage, which may indicate that the flocculus is required for initiation (although not for maintenance) of the compensatory process following the induction of peripheral lesions. Courjon et al.\(^5\) reported that normal cats subjected to hemilabyrinthectomy compensated in about 2 months, whereas previously hemifloculectomized cats are still very poorly compensated 2 to 3 months after hemilabyrinthectomy.

During the 4 weeks to 10 months after hemilabyrinthectomy (during the compensatory stage), the rate of LCGU in the deafferented vestibular nuclei equaled that of the intact side. In a study by Precht et al.,\(^23\) during compensation of vestibulo-ocular function the frequencies of spontaneous discharges by type 1 neurons on the destroyed side were still lower than those on the intact side. This might be responsible for the incomplete recovery of postural asymmetry. Their animals were not, in fact, in the compensatory stage. A major issue is defining the systems and mechanisms by which vestibular balance is restored. The reappearance of spontaneous discharges of type 1 neurons after degeneration of primary excitatory sensory input may be caused by biochemical sensitization of deafferented type 1 neurons or by sprouting of other afferent fibers, such as those related to reticulo-vestibular connections.\(^23\) Dieringer and Precht\(^6\) reported that neurons in the partially deafferented nuclei in chronic preparations (hemilabyrinthectomized frogs) showed increased excitability and increased synaptic efficacy in commissural transmission. More recently, Galiana et al.\(^10\) demonstrated that commissural pathways connecting the two sides of the brainstem are putatively powerful adaptive modulators of the static characteristics of vestibular responses. Our observations of behavior in the present study showed that, in fully compensated cats, interruption of the vestibular crossed connections through reticular and cerebellar pathways\(^8,27\) resulted in reappearance of the symptoms observed immediately after production of a unilateral lesion. Bienhold and Flohr\(^28\) reported similar observations following comissurectomy in fully compensated frogs. On the other hand, Smith et al.\(^28\) studied the effects of comissurectomy in hemilabyrinthectomized guinea pigs with an intact cerebellum. They demonstrated that postural symptoms were compensated in the absence of the (trans-recticular) vestibular commissures. In the present study, the vermis, fastigial nuclei, and surrounding white matter were aspirated to interrupt the trans-cerebellar inhibitory interaction between the bilateral vestibular nuclei. Thus, both the trans-recticular and transcerebellar crossed pathways linking the bilateral vestibular nuclei were interrupted. When the only lesion in cerebellum, vestibular compensation is greatly delayed when the vermis and fastigial nuclei are involved. Therefore, further study is required to determine whether these cerebellar areas contribute to the overall system of crossed pathways linking the bilateral vestibular nuclei or whether they make another contribution to the compensatory process.

The compensatory stage is marked by increased activity in nuclei reticularis parvocellularis, gigantocellularis, and lateralis, superior colliculus, posterior vermis, nodulus, and cerebellar nuclei. This supports the hypothesis that vestibular compensation results from the combined activity of many brainstem and cerebellar structures. Following the loss of primary afferent input to the vestibular nuclei, the level of spontaneous activity is severely decreased and symmetry of function is lost. As the animal returns to normal functioning, there is a proportionate increase in activity in the deafferented vestibular nuclei and in other structures. In vestibular compensation, input from the intact labyrinth may contribute to this reconstruction, and information derived from other sensory systems may also be important. Information from muscle, joint, and cutaneous afferents would first be integrated in the brainstem prevestibular nuclei and then proceed to the vestibular and cerebellar nuclei.\(^16\) Descending stimuli from the cerebral cortex and visual centers, including the visuo-tectal system, would influence the activity of vestibular neurons as well. According to Putkonen et al.,\(^24\) static visual input is a necessary condition for compensation of the postural deficits of hemilabyrinthectomy in the cat. Maintenance of stable head position also depends upon continuous availability of visual input. All of these systems may modulate the output of vestibular neurons by increasing activity in such a way as to correct for the postural and oculomotor abnormalities.

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Address reprint requests to: M. Maeda, M.D., Department of Neurosurgery and Casualty Center, Juntendo University Izunagaoka Hospital, 1,129 Izunagaoka, Tagata-gun, Shizuoka 410-22, Japan.