Archives Italiennes de Biologie, *131*: 173-190, 1993.

ROLE OF NMDA RECEPTORS IN LESION-INDUCED PLASTICITY

H. FLOHR AND U. LÜNEBURG

Brain Research Institute, University of Bremen, NW2, P.O.B. 330 440, D-2800 Bremen 33, Germany

INTRODUCTION

Sensorimotor systems react to both central and peripheral lesions with plastic changes. These changes are *adaptive* and lead to a partial or complete restitution of the initially disrupted functions. Since the first observations by Flourens (25) and Bechterew (2), *vestibular compensation*, the process of functional recovery following unilateral vestibular lesions, has been regarded as an especially attractive model for the study of these recovery phenomena. It is probably the most extensively investigated model for this type of plasticity (24, 34, 35, 44, 45, 51, 55, 61, 62).

Hemilabyrinthectomy (HL) or transection of the VIIIth nerve disturbes the performance of the vestibulo-ocular, vestibulo-collic and vestibulo-spinal reflexes, and causes a severe disturbance of an organism's orientation in space. Both, static and dynamic symptoms can be distinguished. The static symptoms are attributable to the resultant asymmetry in the tonic influences exerted by the vestibular system on the musculature of head, body and eyes. They manifest themselves in an abnormal head position, an asymmetrical body posture and (in some species) a spontaneous ocular nystagmus. The dynamic symptoms are caused by asymmetries in the gain of dynamic reflexes which occur as a result of head movement. They manifest themselves as abnormalities in the amplitude and timing of the vestibulo-ocular and vestibulo-spinal reflexes leading, in particular, to disturbances in the stabilization of visual coordinates during self-motion.

Both, static and dynamic deficits disappear with time. This recovery process has been observed in all species investigated to date: in fish, amphibia, birds and mammals, including man (24, 51). Although the vestibular lesion syndrome is basically similar in all vertebrates, large interspecific differences are found in rate, extent and order of how different symptoms are compensated. Probably, different strategies at the neuronal or system's level are used to obtain the same goal, i.e. recovery of overall vestibular functions.

Since the lesioned labyrinth does not regenerate, unilateral labyrinthectomy results in a permanent loss of inputs from the lesioned side. Compensation must therefore consist in a reorganization of central structures (39). In this process, the functional meaning of the remaining inputs from a variety of sensory sources must be redefined by the system. This modification of a multisensory integration process is — somewhat simplifying — termed *sensory substitution* (34, 61, 62). It is assumed that during compensation, the effectiveness of other inputs to the partially

deafferented vestibular nuclear complex is enhanced, e. g. by those from the visual and somatosensory systems or from the intact contralateral labyrinth, and that these afferents functionally take over the role of the lost labyrinthine inputs. It is further assumed that this sensory substitution is caused by *local* mechanisms which occur as a direct consequence of the partial deafferentation of the vestibular neurons, ipsilateral to the lesion. Three types of possible local reactions have been discussed (cf. 55): 1) *postsynaptic supersensitivity*, i.e. an increase in affinity and/or number of receptor sites as often observed in other areas of the CNS following partial denervation; 2) *collateral sprouting* induced by local changes in the concentration of tropic factors regulating competition for the target neuron; 3) *changes in membrane properties* following deafferentation which alter the resting activity of vestibular neurons.

The fundamental problem of this concept is that the suggested neuronal mechanisms offer no explanation for the adaptive, goal-directed character of compensation processes (21, 22, 24). The establishment of new, functionally adequate circuits would require *specific* modifications in a complex network. It is difficult to see how the local reactions mentioned above could achieve this *per se*. Collateral sprouting or postsynaptic supersensitivity would not automatically have a «debugging» effect. They could just as easily be indifferent or even functionally detremental and «tend towards relative chaos without guidance of behavioural control» (41). Describing compensatory processes as adaptive implies an intentional ascription. A system is postulated that observes itself, recognizes errors and adjusts the system to some goal. Cognitive capacities are a prerequisite of adaption. Such doubts are supported by two arguments. Firstly, there is convincing experimental evidence that the compensation process is not, or not only, caused by the deafferentation of the vestibular neurons. The initiation and rate of the compensation process depend on the state of other sensory systems relevant for spatial orientation (24, 28, 34, 62). An additional modification of the performance of these systems, such as visual deprivation or altered proprioceptive inputs, has a pronounced effect on the course of compensation. The process is context-dependent although the *local* consequences of the lesion remain the same in different contexts.

Secondly, such an explanation cannot account for the similarity between lesion-induced plasticity and those compensatory processes induced by rearrangement of sensory signals without invasive interference, e.g. maintained optical modification of vision by prisms or microgravity (3).

It has been shown recently that the activation of N-methyl-D-aspartate (NMDA) receptors is involved in vestibular compensation (15, 17, 36, 37, 43, 50, 54). Administration of competitive and non-competitive NMDA receptor antagonists delays the acquisition of a compensated state (15, 36, 37, 43, 50, 54). Such antagonists also can reverse the compensated state and induce decompensation (17, 36, 37, 54).

The NMDA receptor channel complex was initially studied in connection with long-term potentiation (9, 10, 59) and is obviously involved in various other forms of plasticity (10, 11, 12, 47, 58).

The receptor is both ligand- and voltage-gated, i.e. it can only be activated

by a transmitter binding to the receptor when the postsynaptic membrane is sufficiently depolarized. The receptor-linked channel is permeable to Na^+, K^+ and Ca^{2+} ions. Ca^{2+} triggers a number of molecular changes inside the postsynaptic terminal that permanently modify synaptic efficacy. The strength of this synapse depends on coinciding pre- and postsynaptic activity. This is exactly the kind of conjunctive mechanism required for the implementation of the Hebb algorithm. It is, therefore, assumed that the NMDA receptor channel complex serves as a molecular mechanism for Hebb-type plasticity (12).

Much in accordance with Hebb's original intuitions (27), recent research on synthetic parallel processing systems has revealed that the presence of Hebb synapses endows neural nets with the capacity to learn, i.e. to gain information about the regularities of the outside world, store it as internal representations and use it for the control of the system's performance.

Against this background, the finding that NMDA synapses are involved may lead to a new explanatory concept of adaptive lesion-induced plastic processes: it could be the result of a self-organizing process in neuronal nets using a Hebbian algorithm to organize the strength of connections.

This study has two aims. One is to describe experiments conducted to examine the effects of the NMDA receptor antagonist ({(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate})(MK-801) on the acquisition and maintenance of a compensated state. MK-801 is a non-competitive NMDA receptor channel antagonist, that has a binding site within the ion channel associated with the receptor. It is highly potent and selective for the NMDA receptor having only minimal effects on other glutamate receptor types. It blocks the activation of the receptor (cf. 59).

The second aim is to outline (in a qualitative, non-analytical form) a theoretical framework for compensation processes that, in particular, explains in a non-trivial way how local synaptic changes restore a system's cognitive capacity after a reduction of its sensory surface.

The experiments were performed employing two species, fish and frog, which are believed to possess different mechanisms and strategies (cf. 5, 6, 7) to achieve compensation following unilateral labyrinthectomy.

EXPERIMENTAL STUDIES ON THE EFFECTS OF MK-801 ON THE ACQUISITION AND MAINTENANCE OF A COMPENSATED STATE

1. *MK-801 effects on compensation in* Rana temporaria. — In the grass frog, HL causes static and dynamic symptoms similar to those found in other vertebrates and mammals. As with other species, the initial stage of severe symptoms is followed by a recovery of functions. The postural symptoms are extensively compensated, whereas the dynamic deficits recover less completely. In the present study, compensation of the main postural symptom, head deviation, was chosen to assay the pharmacological effects of MK-801. In the grass frog, HL leads to an initial

head deviation of 29±4 degrees. The time course of compensation follows an exponential function; half compensation (i.e. the time in which the initial head deviation is reduced by 50%) is reached in about 11 days (Fig. 1).

METHODS

The experiments were carried out on common grass frogs (*Rana temporaria*) weighing 20-40 g, kept in small groups in semiaquatic environments in a room illuminated on a 14 h light/10 h dark cycle at a temperature of 20±2°C. Unilateral labyrinthectomy was performed under MS 222 anesthesia as described by Ewald (20). MK-801 was dissolved in frog Ringer solution and the various doses were all injected in a volume of 17 ml/kg (which corresponds to an injection volume of approximately 0.5 ml per animal) into the dorsal lymph sac. To quantify the degree of compensation or drug-induced decompensation, head deviation was measured using specially adapted video equipment. Two series of experiments were performed. In the first series, the effects of chronic post-operative treatment with MK-801 on the *acquisition* of a compensated state was investigated. MK-801 was administered daily from the first to the 14th post-operative day in two doses (0.5 or 2.0 mg/kg/day). Control animals received the frog Ringer vehicle only. The number of animals (n) was 12 in all groups. In the second series, the effect of MK-801 on the *maintenance* of the compensated state was investigated. MK-801 treatment (2.0 mg/kg/day) was begun after different post-lesion intervals: on day 14 (n=10), 28 (n=10), 42 (n=9), 56 (n=7), 70 (n=7), 84 (n=7), 98 (n=6) and 166 (n=15). In each group treatment was continued for the next three days.

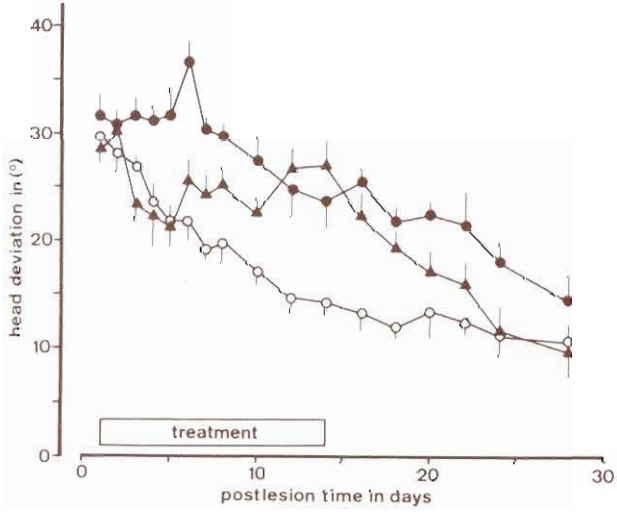

Fig. 1 – *Effect of the NMDA receptor antagonist MK-801 on vestibular compensation following unilateral labyrinthectomy in the grass frog.*

MK-801 was administered daily from the first to the 14th post-operative day in two different doses. Solid triangles: 0.5 mg/kg/day; solid circles: 2.0 mg/kg/day; open circles: Ringer-treated control group. n=12 in all groups. Ordinate: mean values of head deviation in degrees (± S.E.). Abscissa: post-lesion time in days.

RESULTS

a) *Acquisition experiments.* — MK-801 treatment of hemilabyrinthectomized animals beginning with the first post-operative day resulted in a distinct *inhibition of the compensation process.* This effect was dose-dependent (Fig. 1). After cessation of MK-801 treatment on the 14th post-operative day, a further slightly faster compensation took place, so that the compensation level of the Ringer-injected control group was achieved after about two more weeks (Fig. 1).

b) *Maintenance experiments.* — In partly compensated animals, MK-801, injected in a dose of 2.0 mg/kg/day for four consecutive days, caused a marked *decompensation*, i.e. a significant re-increase in head deviation to the lesioned side (Fig. 2). This effect was recognizable 3-4 hours following the injection and persisted in all cases till the following day, when the next injection was made. On cessation of daily MK-801 treatment, head deviation slowly decreased again to the levels of Ringer-treated control animals. The susceptibility of the compensated state, however, progressively decreases with increasing post-lesion time. At post-operative day 56, 70, 84, 98 or 166, this decompensatory effect of MK-801 was no longer observable (Figs. 2 and 3).

2. *MK-801 effects on compensation in* Carassius auratus. — In the goldfish, HL causes severe postural and locomotor symptoms such as flexion of the body, tonic deviation of the eyes, abnormal displacement of the fins and rotation around the longitudinal body axis during locomotion (5, 6). In this species the post-operative deficiencies are compensated with a rapidity not encountered in other vertebrates. Static and dynamic deficits disappear more or less simultaneously within 10 minutes (5, 6).

METHODS

The experiments were performed on common goldfish (*Carassius auratus*), 8-10 cm in length. The animals were kept in small plastic tanks (20 l) in a room illuminated in a 14 h light/10 h dark cycle at a room temperature of $18 \pm 1°C$. Unilateral labyrinthectomy was carried out under MS 222 anesthesia. By using a dorsal approach, the utricular pouch containing the otolith and sensory macula, was removed together with the ampullae of the anterior vertical and horizontal canals and innervating branches from the anterior root of the VIIIth cranial nerve (5). Post-operative recordings of posture and locomotion were made with a color video camera. Following Burt and Flohr (5, 6), animal posture and locomotion was considered impaired when at least one of the symptoms was present; animal posture and locomotion was considered unimpaired when *all* of the above mentioned symptoms were absent. The criterion for successful compensation after HL was the completion of 5 minutes continuous and unimpaired swimming. Animals that fulfill this free-swimming criterion (FSC) showed no further impairment (for details on the technique of measurement see 5, 6). MK-801 was dissolved in fish Ringer solution: the various doses were each injected in a volume of 10 µl. The injections were made into the third ventricle adopting a technique described by Schmidt and Lapp (53). Two series of experiments were performed. In the first series, the effects of MK-801 treatment on the *acquisition*

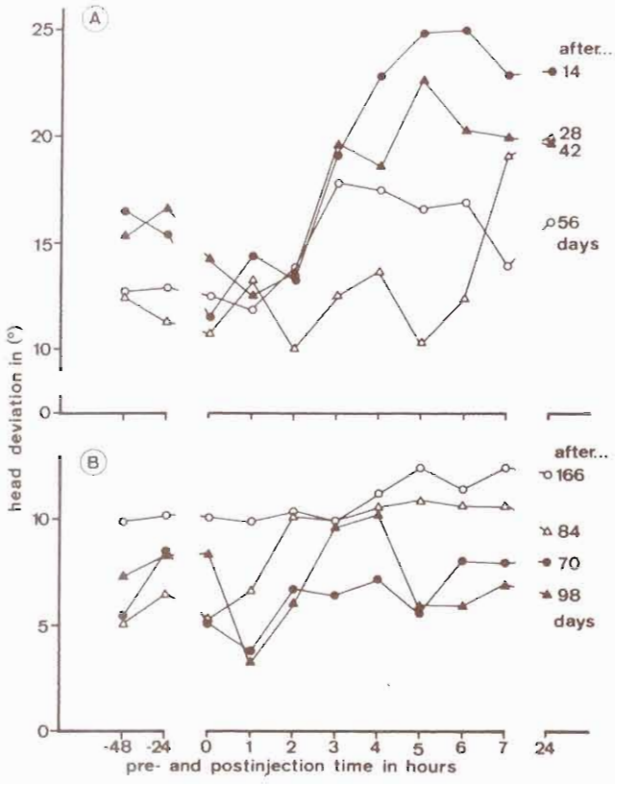

Fig. 2 – *Decompensatory effect of a single injection of 2.0 mg/kg of MK-801 on partly compensated grass frogs.*

A: effect of MK-801 in the «*early*» phase of compensation (injections made 14, 28, 42, or 56 days after unilateral labyrinthectomy, see column on the right). *B*: effect of MK-801 in the «*late*» phase of compensation (injections 70, 84, 98, or 166 days after unilateral labyrinthectomy, see column on the right). For number of animals see Fig. 4. Ordinate: mean values of head deviation in degrees. Abscissa: pre- and post-injection time in hours; «O» indicates the time of injection.

of a compensated state was investigated. Animals received a single intracerebroventricular (icv) injection 1 hour prior to HL. Three doses (2.5, 10 and 20 µg) were tested. Control animals received an injection of fish Ringer. In the second series, the effects of MK-801 on the *maintenance* of the compensated state was investigated. Hemilabyrinthectomized fish were first allowed to compensate; MK-801 (10 µg) was icv injected following 1, 2, 4, 6 and 90 days after HL. Following the MK-801 injection, the animals were returned to the observation tank and their behaviour was videotaped. Control animals were treated identically, except that they received a 10 µl fish Ringer injection.

RESULTS

a) *Acquisition experiments.* — MK-801 treatment 1 hour prior to HL exerted a marked influence on the rate at which the acute vestibular syndrome disappeared.

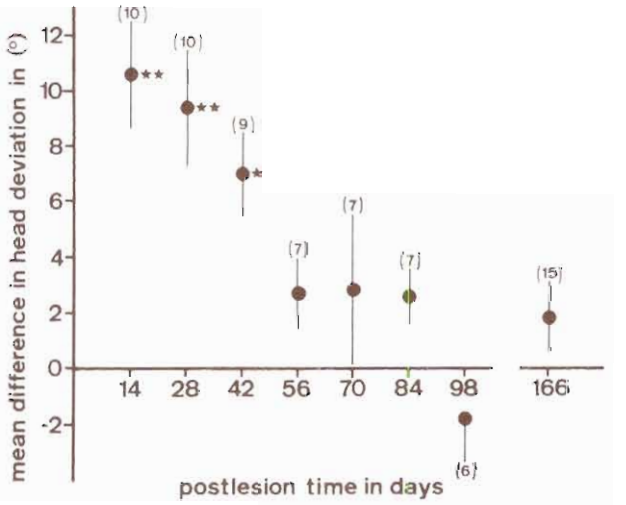

Fig. 3 – *Decompensatory effect of a single injection of 2.0 mg/kg of MK-801 on the grass frog plotted as a function of the time interval between hemilabyrinthectomy and MK-801 administration.*

Ordinate: mean *difference* in head deviation in degrees (± S.E.) measured *immediately before and 24 hours after* the injection of MK-801. Abscissa: post-lesion time in days. Number of animals in parentheses. Original data were tested for significance by Welch's t-test, two-tailed analysis: ** = $2P < 0.001$, * = $2P < 0.01$.

Ringer-treated animals reached the criterion for successful compensation (FSC) within 10 *minutes*, whereas in MK-801-treated animals the time to criterion was increased in a dose-dependent manner: 2.5 μg MK-801 increased the time to criterion to 8.6 ± 4.9 *hours*, 20 μg MK-801 increased it to a value of 13.7 ± 3.5 *hours* (Fig. 4).

b) *Maintenance experiments.* — Up to 2 days after HL, a single icv-injection of MK-801 (10 μg) induced decompensation, i.e. the reappearance of *all* symptoms characteristic for the acute state (Figs. 5 and 6). Decompensation began immediately after the injection. The effect was transient, the duration is varying considerably among individual animals. All symptoms were reversed after 24 hours (Fig. 5). In contrast, the same MK-801 treatment of compensated animals performed 4, 6 or 90 days after HL did *not* cause decompensation. After these intervals, no signs of an impaired locomotion or posture could be observed (Fig. 6). In control animals, injected with fish Ringer solution, no decompensatory effect was found at any post-lesion interval.

DISCUSSION

The bilateral vestibular nuclei play a crucial role in the compensation process. These nuclei which project to ocular and spinal motoneurons constitute an integrating structure important to all sensory systems involved in spatial orientation.

Vestibular, visual and proprioceptive afferents converge bilaterally as primary

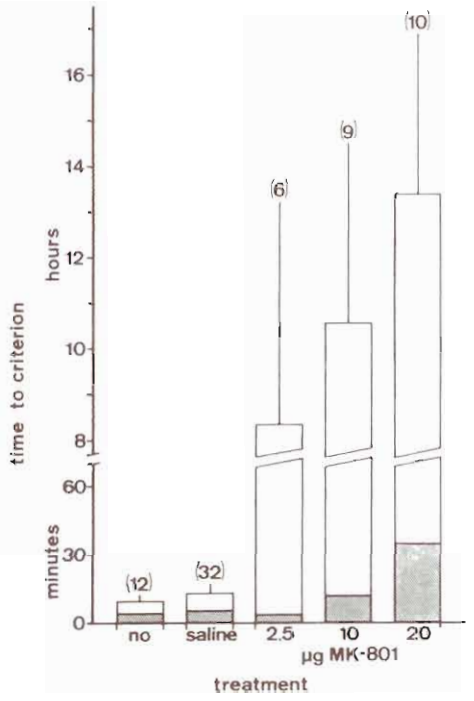

Fig. 4 – *Effect of different doses (2.5, 10, or 20 µg) of MK-801 on the time to achieve compensation in the goldfish.*

Intracerebroventricular injections of MK-801, made 1 hour prior to hemilabyrinthectomy, are contrasted to those of the fish Ringer vehicle. Columns indicate the mean time (+ S.E.) to fulfill the FSC criterion. Hatched area demonstrates the time span between replacing the fish back to the observation tank and the onset of body movements in the different experimental groups. Number of animals in parentheses.

or higher order projections in the vestibular nuclei, the latter representing a potential structure for the reorganization of this multimodal system. Following unilateral labyrinthectomy, the resting discharge of the ipsilateral vestibular neurons is depressed, whereas that of neurons on the intact side remains unchanged or is enhanced (18; cf. 24, 55). This imbalance in activity is responsible for the postural and dynamic deficits.

During the course of compensation, the tonic activity on the deafferented side is restored, so that the imbalance in bilateral activity is reduced (24, 55). It is assumed that this regeneration of resting activity can be derived from several sources, including a number of sensory systems. The contribution of somatosensory (1, 29, 33, 42) and visual (5, 6, 13, 14, 46) as well as commissural vestibular afferents from the intact contralateral labyrinth (4, 18, 19, 38, 60) is well documented, and has led to the sensory substitution concept. This concept is supported by two kinds of observations: firstly, after successful compensation, other sensory systems exert a stronger influence on the vestibular reflexes, and, secondly, elimination of such inputs can cause decompensation (1, 6, 34, 62). Different species use different strategies for sensory substitution. In the goldfish, the first phase

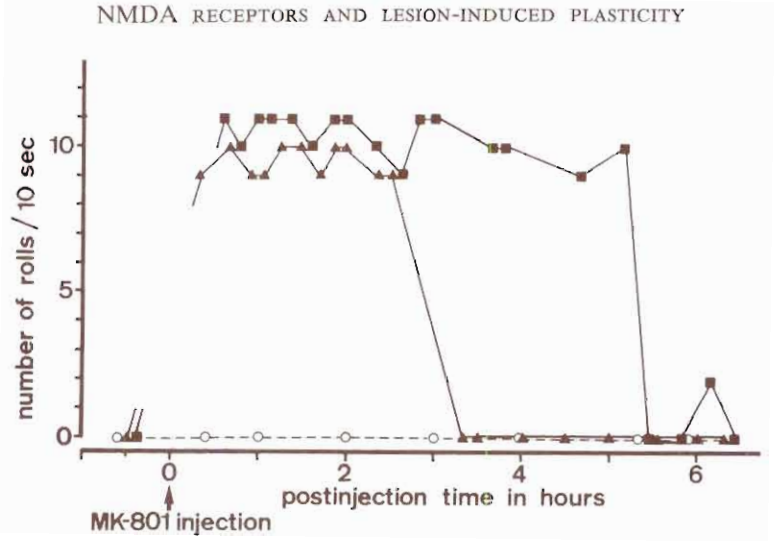

Fig. 5 – *Decompensatory effect of a single icv-injection of 10 µg MK-801 on swimming behaviour of compensated goldfish 2 days after hemilabyrinthectomy.*

The number of rotations per 10 seconds of swimming is shown as an indicator for the duration of decompensation. Examples of two animals treated with MK-801 (solid squares and triangles) and one control animal (also 2 days after HL) treated with the fish Ringer vehicle (open circles).

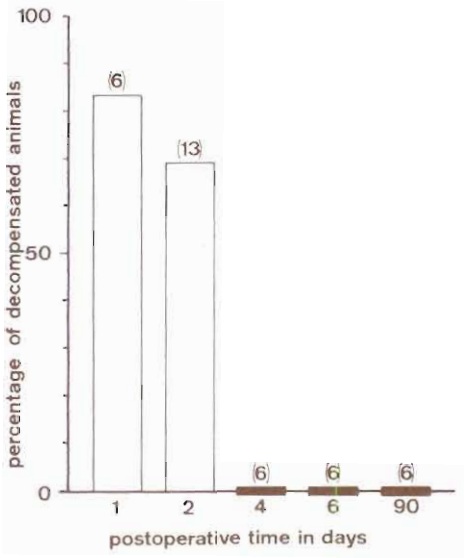

Fig. 6 – *Decompensatory effect of a single icv-injection of 10 µg MK-801 on the goldfish as a function of post-lesion time.*

Injections of MK-801 were made 1, 2, 4, 6, or 90 days after hemilabyrinthectomy. Columns indicate the percentage of animals of the individual groups which show decompensatory symptoms lasting for *more than 1 hour* after injection of MK-801. Number of animals in parentheses. Icv-injections of fish Ringer solution did not have any decompensatory effect at any of the above time interval (results not shown).

of recovery is regarded to be based on a visual substitution process (5, 6). In the frog, the intervestibular commissural system probably plays an essential role. In this species compensation is correlated with an increase in the efficacy of brainstem commissural inputs to the deafferented vestibular nucleus (18, 19); a destruction of these fibers is followed by decompensation (4).

The processing of information depends on various transmitter systems that exist within the vestibular nuclei (cf. 16, 48, 56). Fig. 7 summarizes the information presently available from pharmacological and electrophysiological studies in the frog. As can be seen, the NMDA receptor subtype is present at different sites, in particular in the intervestibular commissures. The possible role of commissural NMDA synapses in relation to vestibular compensation was first investigated by Cochran *et al.* (8), Knöpfel (31) and Knöpfel and Dieringer (32). Using brainstem *in vitro* preparations from fully compensated frogs, they concluded that NMDA receptors do *not* contribute to the altered commissural inputs to the deafferented vestibular neurons. The observations of Raymond *et al.* (49) support this conclusion. These authors did not find an increase in glutamate receptor binding in the deafferented vestibular nucleus of compensated rats, relative to the VN of the intact side and uncompensated animals. These findings, however, do not exclude the possibility that the NMDA synapse contributes to the *acquisition* of a compensated state, or is responsible for early phases of compensation. This is indeed suggested by the present findings. NMDA receptors perform a transient function in the acquisition process, but not in the maintenance of the compensated

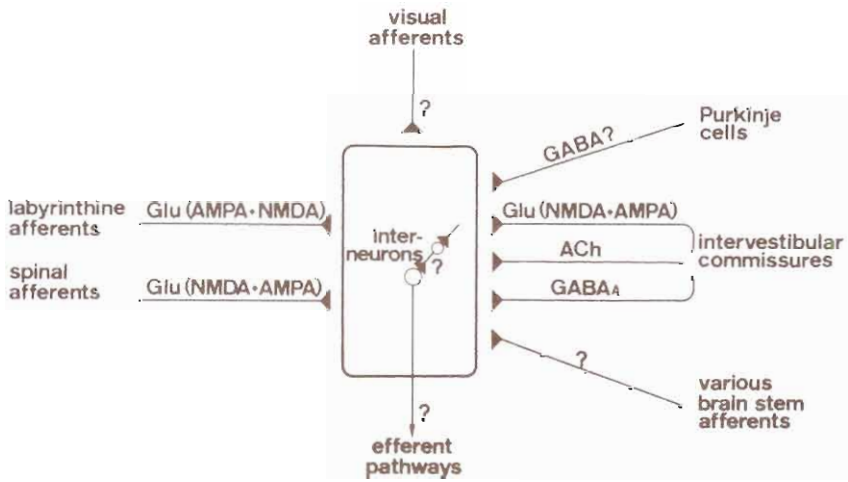

Fig. 7 – *Schematic diagram of neuronal afferents to the vestibular nuclear complex (VNC) of the frog and the neurotransmitters involved.*

The transmitter of primary labyrinthine afferents is an excitatory amino acid (glutamate and/or aspartate), the action of which is mainly mediated by AMPA receptors (8, 31, 32). Spinal and intervestibular commissural afferents also use an excitatory amino acid; in this case its action is mediated to a great extent by NMDA receptors (8, 31, 32). In addition, commissural afferents are mediated by cholinergic (30) and GABAergic (19) transmitter systems. A question mark indicates that the transmitter(s) are either uncertain or unidentified.

state. According to the present findings, two stages must be assumed: a MK-801-sensitive phase in which NMDA receptors do contribute to compensation and a late phase in which they do not. The late phase is achieved by going through the MK-801-sensitive phase. If the early phase is disturbed, the acquisition of the late phase will be delayed. In the goldfish, the MK-801-sensitive phase lasts for about 2 days. In this species, two phases have been distinguished: an 'acute' phase based on a visual substitution process and a 'late' phase which is independent of visual cues (6, 7). The duration of the acute phase, as was measured in these experiments, corresponds well with the duration of the MK-801-sensitive period.

Smith and Darlington (54), Darlington and Smith (15) and Sansom *et al.* (50) arrived at similar results in recent studies employing guinea pigs. In this species, NMDA receptor antagonists interfere with vestibular compensation during a period of approximately one week. Thereafter, this effect is no longer obtainable. From these studies, with MK-801 injected either systematically or intraventricularly, it is impossible to definitely locate the site of action. However, as discussed by Smith and Darlington (56), it is improbable that the effects on compensation are due to the anesthetic effects of MK-801. It is also unlikely that the observed effects could be a consequence of an impaired retinotectal transmission. Intact frog and fish, treated with MK-801 in the aforementioned doses, do not display any alteration in their optomotor behaviour, when tested in the optomotor drum deviced by Springer *et al.* (57), (Lüneburg and Flohr, unpublished). In addition, MK-801-treated fish exhibited a normal dorsal light response (Lüneburg and Flohr, unpublished). The latter findings are confirmed by recent observations by Schmidt (52). Such side effects are also improbable because of the differences in MK-801 action observed in early and late phases of the compensation process. In accordance to this, observations made by De Waele *et al.* (17) suggest a direct action of the drug on vestibular neurons of the lesioned side.

These authors, also using guinea pigs in their experiments, found that the NMDA antagonist D-APV caused a decompensation when it was directly injected into the deafferented vestibular nucleus six days after HL.

In contrast to Knöpfel and Dieringer (32) and Raymond (49), De Waele *et al.* (17) speculated that denervation supersensitivity resulting from an increase in either the number and/or the sensitivity of NMDA receptors might be responsible for compensation.

Such an NMDA supersensitivity hypothesis, however, cannot be positively confirmed by the present findings. Instead, a transient role of NMDA receptors, similar to that discussed in long-term potentiation (LTP) would comply to the experimental data. In LTP the NMDA receptor has an essential function in the induction, but not in the maintenance of the plastic changes involved. It is assumed that the activation of NMDA receptors results in an increse in intracellular Ca^{2+} which then triggers a number of Ca^{2+}-dependent changes inside the postsynaptic terminal. Ca^{2+} regulates the function of channel proteins and several cytosolic proteins, including protein kinases, phosphatases and proteases which, in turn, affect the excitability of the postsynaptic membrane. It also influences neuronal

protein synthesis directly and indirectly. These changes could ultimately modify the efficacy of both NMDA synapses and non-NMDA synapses (59).

LOCAL MECHANISMS AND ADAPTATIVE REORGANIZATION OF SENSORIMOTOR SYSTEMS: A HYPOTHESIS

In the following we specify a hypothesis on the role of the NMDA receptor in vestibular compensation, analogous to that assumed in LTP, more precisely.

It is assumed (Fig. 8a and b) that the vestibular neurons figure as elements in a diffusely interconnected net and receive redundant multimodal afferents from various sensory surfaces. Some of these afferents are always mediated by NMDA synapses. If the neuron is partially deafferented, all remaining afferents will undergo a reweighting process. According to the Hebb-principle, those synapses would increase weight that carry coincident activity.

In a neuron which receives redundant information on an external event from different sensory sources by NMDA and non-NMDA synapses, the NMDA-receptor-channel-mediated mechanisms would have two successive effects. Firstly, in the acute phase following HL, it will amplify the effect of cooperating synapses by opening NMDA channels postsynaptically, if a threshold activation is reached by coinciding presynaptic activity. The functional role of the neuron would be restored at a dynamic basis (Fig. 9). Secondly, repeated activation of the NMDA channel would, via Ca^{2+}, induce long-term modifications of those synapses that cooperate regularly. Their weight would be permanently enhanced, the weighting process being guided by the coincidence detector. Both, acute and long-term mechanisms would inevitably strengthen those synapses that have the same representational content, and only enhance inputs with information equivalent to that of the lost input channel. The functional role of the partially deafferented neuron would be restored by using different sensory cues (Fig. 9).

'Conflicting' afferents would be suppressed. The sensory substitution would be selective. Thus, the system learns in an unsupervised mode to use redundant information from overlapping sensory systems to compensate for deficiencies in one system. Treating lesion-induced plastic processes as a self-organizing process in a neuronal net consequently would explain how new cognitive capacities emerge from local synaptic changes. Such a selection process could also control sprouting. Sprouts would not diffusely occupy vacated spaces, instead they underly a local selection according to their information content.

It is assumed here that plastic changes can be produced in non-NMDA synapses by these mechanisms. This would explain why compensation is sensitive to NMDA antagonists in early, but not in late phases of the compensation process. This assumption is also in accordance with a number of observations showing that, in late stages, different (non-NMDA) transmitter systems, such as cholinergic, adrenergic and GABA-ergic, contribute to the maintenance of the compensated state. This state is susceptible to the administration of various neurotransmitter

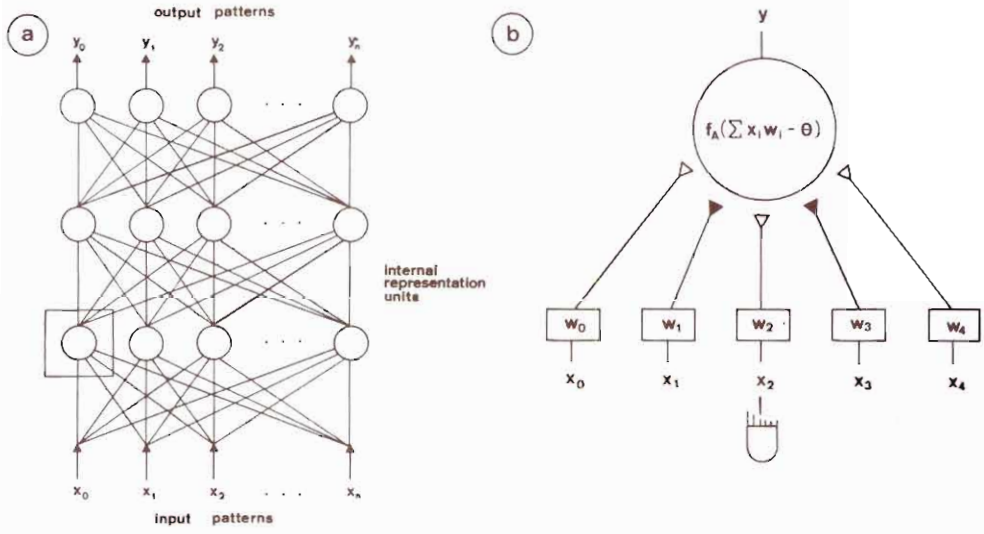

Fig. 8 – *Schematic representation of the interconnected net of vestibular nuclear neurons.*

It is assumed that the vestibular neurons figure as units in a diffusely interconnected net and receive *redundant* inputs from the sensory surface (*a*). In *b* one unit from the internal representation layers is magnified. The input vectors (x_0, x_1, x_2...) are transmitted by connections with different weighting factors (w_0, w_1, w_2...). Some of these inputs are mediated by NMDA receptors (solid triangles), others by non-NMDA receptors (open triangles). f_A, activation function; Θ, threshold; y, output vector.

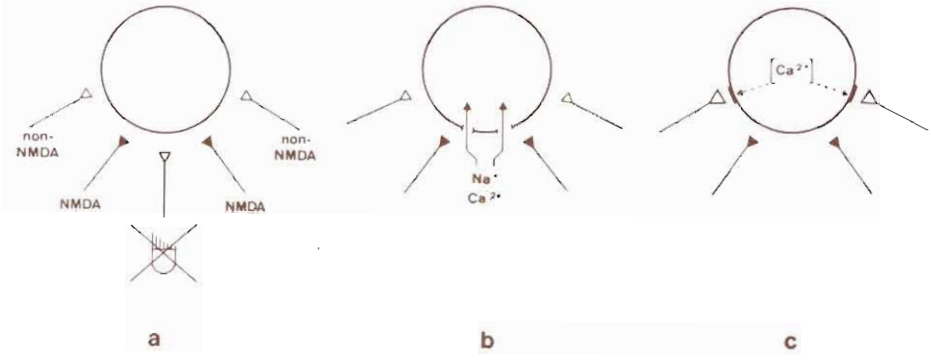

Fig. 9 – *Same neuron as in Fig. 8*b, *shown in three different situations.*

a) After labyrinthine deafferentation; y is decreased.

b) In the MK-801-sensitive phase of compensation. Coincident input at remaining NMDA (solid triangles) and non-NMDA (open triangles) synapses has led to an activation of the NMDA receptor channel complex amplifying the depolarizing effects of coincident inputs. f_A is transiently changed and the functional role of the neuron within the net is restored on a dynamic basis.

c) In the MK-801-insensitive phase of compensation. Repeated activation of NMDA receptor associated channels and increase in intracellular $[Ca^{2+}]$ has induced long-term modifications of neighbouring synapses, w_0 and w_4, (large open triangles). y is restored as a result of sensory substitution.

agonists and antagonists. Two syndromes can be distinguished: *decompensation*, consisting in a reappearance of symptoms characteristic of the acute stage, and *overcompensation*, comprising (Bechterew-like) static and dynamic symptoms opposite to those observed in the acute stage. The interpretation that has been given to those observations was that the (chronically) compensated state is attributable to the development of supersensitivity in the deafferented vestibular nuclei in different transmitter systems (23, 24).

As can be further seen from Fig. 8a, the principle of substitution would also endow the system with a hierarchy of different strategies for compensation. Substitution could *not* only occur at the first sensory layer, but also at more abstract levels of representation. From Fig. 8a it is evident that, by the same procedure, a lost *function* could be replaced by a new pattern of internal states, producing an output similar or identical to that initially abolished. The system would thus be enabled to compensate for a lesion in a subsystem A by substituting a mechanicistically different and functionally synergistic mode B to produce the same output. Unsupervised learning procedures in such networks could, therefore, explain compensatory processes at the functional level (34, 62).

Connectionist learning procedures can be divided into three broad classes. In *unsupervised procedures*, as discussed above, the system captures regularities in their input vectors. The system can develop representations of higher-order invariances of the surrounding world as a result of merely repeating the exposure. *Supervised procedures* require a teacher to explicitly specify the correct output state for any given input state to the network. The network then compares the output which is produced by an input to the desired output, and uses this difference in activation to modify the weights in the network. *Reinforcement* learning procedures require a yes-or-no evaluation of the output. Hebb-like algorithms are essential in all three learning procedures. The present hypothesis that compensation originates from unsupervised procedures, therefore, is the most parsimonious interpretation, but is by no means the only one possible.

Different types of connectionist learning procedures could coexist and cooperate in real systems and endow the system with a number of different strategies to achieve compensation, as it is in fact suggested by numerous observations on the behaviour of lesioned systems (26, 40).

SUMMARY

The effect of the N-methyl-D-aspartate (NMDA) receptor antagonist MK-801 on the acquisition and maintenance of a compensated state following unilateral labyrinthectomy was investigated in two species, grass frog and goldfish. MK-801: 1) inhibits the acquisition of a compensated state, and 2) causes a loss of compensation in early phases of the compensation process, but 3) has no such effect to the long-term maintenance of compensation. It is concluded that NMDA receptors perform a *transient* function by inducing a sensory or functional substitution process

in the deafferented vestibular system. A hypothesis is presented explaining the lesion-induced adaptive process as a result of a self-organizing process in a neural net using Hebb-like algorithms to organize the strength of connections.

Acknowledgement. — This work was supported by the Deutsche Forschungsgemeinschaft (Fl 139/4-2).

REFERENCES

1. AZZENA, G. B. Role of the spinal cord in compensating the effects of hemilabyrinthectomy. *Arch. Ital. Biol.*, **107**: 43-53, 1969.
2. BECHTEREW VON, W. Ergebnisse der Durchschneidung des N. acusticus, nebst Erörterung der Bedeutung der semicirculären Canäle für das Körpergleichgewicht. *Pflügers Arch.*, **30**: 312-347, 1883.
3. BERTHOZ, A. and MELVILLE JONES, G. (Eds.) *Adaptive Mechanisms in Gaze Control.* Rev. in Oculomot. Res., Vol. 1. Amsterdam, Elsevier, 1985.
4. BIENHOLD, H. and FLOHR, H. Role of commissural connexions between vestibular nuclei in compensation following unilateral labyrinthectomy. *J. Physiol., Lond.*, **248**: 178, 1978.
5. BURT, A. and FLOHR, H. 'Acute' vestibular compensation in the goldfish: a visual substitution process? Pp. 393-410. In: FLOHR, H. (Ed.), *Post-Lesion Neural Plasticity.* Berlin, Heidelberg, New York, Springer, 1988.
6. BURT, A. and FLOHR, H. Role of the visual input in the recovery of function following unilateral vestibular lesion in the goldfish. I. Short-term behavioural changes. *Behav. Brain Res.*, **42**: 201-211, 1991.
7. BURT, A. and FLOHR, H. Role of the visual input in the recovery of function following unilateral vestibular lesion in the goldfish. II. Long-term behavioural changes. *Behav. Brain Res.*, **42**: 213-225, 1991.
8. COCHRAN, S. L., KASIK, P. and PRECHT, W. Pharmacological aspects of excitatory synaptic transmission to second order vestibular neurons in the frog. *Synapse*, **1**: 102-123, 1987.
9. COLLINGRIDGE, G. L. and BLISS, T. V. P. NMDA receptors — their role in long term potentiation. *Trends Neurosci.*, **10**: 288-293, 1987.
10. COLLINGRIDGE, G. L. and LESTER, R. A. Excitatory amino acid receptors in the vertebrate central nervous system. *Pharmacol. Rev.*, **40**: 143-210, 1989.
11. COLLINGRIDGE, G. L. and SINGER, W. Excitatory amino acid receptors and synaptic plasticity. *Trends Pharmacol. Sci.*, **11**: 290-296, 1990.
12. COTMAN, C. W., MONAGHAN, D. T. and GANONG, A. H. Excitatory amino acid neurotransmission: receptors and Hebb-type plasticity. *Ann. Rev. Neurosci.*, **11**: 61-80, 1988.
13. COURJON, J. H. and JEANNEROD, M. Visual substitution of labyrinthine deficits. Pp. 783-792. In GRANIT, R. and POMPEIANO, O. (Eds.), *Reflex Control of Posture and Movement.* Progr. in Brain Res., Vol. 50, Amsterdam, Elsevier, 1969.
14. COURJON, J. H., JEANNEROD, M., OSSUZIO, I. and SCHMID, R. The role of vision in the compensation of vestibulo ocular reflex after hemilabyrinthectomy in the cat. *Exp. Brain Res.*, **28**: 235-248, 1977.
15. DARLINGTON, C. L. and SMITH, P. The effects of NMDA antagonists on the development of vestibular compensation in the guinea pig. *Eur. J. Pharmacol.*, **174**: 273-278, 1989.
16. DE WAELE, C., SERAPHIN, M., MUHLETALER, M. and VIDAL, P.-P. Neurochemical aspects of vestibular compensation. Pp. 95-104. In LACOUR, M., TOUPET, M., DENISE, P. and CHRISTEN, Y. (Eds.), *Vestibular Compensation. Facts, Theories and Clinical Perspectives.* Amsterdam, Elsevier, 1989.

17. De Waele, C., Vibert, N., Beaudrimont, M. and Vidal, P.-P. NMDA receptors contribute to the resting discharge of vestibular neurons in the normal and hemilabyrinthectomized guinea pig. *Exp. Brain Res.*, **81**: 125-133, 1990.
18. Dieringer, N. and Precht, W. Mechanisms of compensation for vestibular deficits in the frog. I. Modification of the excitatory commissural system. *Exp. Brain Res.*, **36**: 311-328, 1979 a.
19. Dieringer, N. and Precht, W. Mechanisms of compensation for vestibular deficits in the frog. II. Modification of inhibitory pathways. *Exp. Brain Res.*, **36**: 329-341, 1979 b.
20. Ewald, J. R. *Physiologische Untersuchungen über das Endorgan des N. octavus*. Wiesbaden, Bergmann, 1892.
21. Flohr, H., Bienhold, H., Abeln, W. and Macskovics, I. Concepts of vestibular compensation. Pp. 153-172. In Flohr, H. and Precht, W. (Eds.), *Lesion-Induced Plasticity in Sensorimotor Systems*. Berlin, Heidelberg, New York, Springer, 1981.
22. Flohr, H. Control of plastic processes. Pp. 60-74. In Basar, E., Flohr, H., Haken, H. and Mandell, A. J. (Eds.), *Synergetics of the Brain*. Springer Series in Synergetics, Vol. 23. Berlin, Heidelberg, New York, Springer, 1983.
23. Flohr, H., Abeln, W. and Lüneburg, U. Neurotransmitter and neuromodulator systems involved in vestibular compensation. pp. 269-277. In Berthoz, A. and Melville Jones, G. (Eds.), *Adaptive Mechanisms in Gaze Control*. Rev. in Oculomot. Res., Vol. 1. Amsterdam, Elsevier, 1985.
24. Flohr, H., Burt, A., Will, U. and Ammelburg, R. Vestibular compensation: a paradigm for lesion-induced neural plasticity. Pp. 243-260. In Rahmann, H. (Ed.), *Fundamentals of Memory Formation: Neuronal Plasticity and Brain Function*. Prog. in Zool., Vol. 37. Berlin, New York, Springer, 1989.
25. Flourens, J. P. N. *Recherches Expérimentales sur les Propriétés et les Fonctions du Système Nerveux dans les Animaux Vertébrés*. Paris, Crevot, 1824.
26. Goldberger, M. E. Motor recovery after lesions. *Trends Neurosci.*, **3**: 288-291, 1980.
27. Hebb, D. O. *The Organization of Behavior*. New York, Wiley, 1949.
28. Igarashi, M. Physical exercise and acceleration of vestibular compensation. Pp. 131-143. In Lacour, M., Toupet, M., Denise, P. and Christen, Y. (Eds.), *Vestibular Compensation. Facts, Theories and Clinical Perspectives*. Amsterdam, Elsevier, 1989.
29. Jensen, D. W. Reflex control of acute postural asymmetry and compensatory symmetry after unilateral vestibular lesions. *Neurosci.*, **4**: 1059-1073, 1979.
30. Kasik, P., Cochran, S. L., Dieringer, N. and Precht, W. Evidence for an alteration in brainstem cholinergic pathways following unilateral labyrinthectomy in the frog. *Brain Res.*, **363**: 188-191, 1986.
31. Knöpfel, T. Evidence for N-methyl-D-aspartic acid receptor mediated modulation of the commissural input to central vestibular neurons in the frog. *Brain Res.*, **426**: 212-224, 1987.
32. Knöpfel, T. and Dieringer, N. Lesion-induced vestibular plasticity in the frog: are N-methyl-D-aspartate receptors involved? *Exp. Brain Res.*, **72**: 129-134, 1988.
33. Lacour, M., Roll, J. P. and Appaix, M. Modification and development of spinal reflexes in the alert baboon (Papio papio) following unilateral vestibular neurotomy. *Brain Res.*, **113**: 255-269, 1976.
34. Lacour, M. Restoration of nerve function. Pp. 11-34. In Lacour, M., Toupet, M., Denise, P. and Christen, Y. (Eds.), *Vestibular Compensation. Facts, Theories and Clinical Perspectives*. Amsterdam, Elsevier, 1989.
35. Lacour, M., Toupet, M., Denise, P. and Christen, Y. (Eds.) *Vestibular Compensation. Facts, Theoreis and Clinical Perspectives*. Amsterdam, Elsevier, 1989.
36. Lüneburg, U. and Flohr, H. Possible role of NMDA receptors in vestibular compensation. P. 178. In Elsner, N. and Roth, G. (Eds.), *Brain, Perception, Cognition*. Stuttgart, New York, Thieme, 1990.

37. LÜNEBURG, U. and FLOHR, H. The NMDA receptor antagonist MK-801 affects vestibular compensation in the goldfish. P. 152. In ELSNER, N. and PENZLIN, H. (Eds.), *Synapse, Transmission, Modulation*. Stuttgart, New York, Thieme, 1991.
38. MAEDA, M. Mechanisms of vestibular compensation in the unilateral labyrinthectomized cat. Pp. 385-394. In POMPEIANO, O. and ALLUM, J. H. J. (Eds.), *Vestibulospinal Control of Posture and Movement*. Progr. in Brain Res., Vol. 76. Amsterdam, Elsevier, 1988.
39. MAGNUS, R. *Körperstellung*. Berlin, Springer, 1924.
40. MARSHALL, J. F. Neuronal plasticity and receovery after nerve injury. Pp. 201-247. In: SMYTHIES, J. R. and BRADLEY, J. (Eds.), *Int. Rev. Neurobiol.*, Vol. 26. Orlando, Academic Press, 1985.
41. MELVILLE JONES, G. Behavioural control of central plasticity: fact or fiction. Pp. 9-13. In: IGARASHI, M. and BLACK, F. O. (Eds.), *Vestibular and Visual Control on Posture and Locomotor Equilibrium*. Basel, Karger, 1985.
42. PETROSINI, L. Compensation of vestibular symptoms in hemilabyrinthectomized guinea pigs. Role of sensorimotor activation. *Behav. Brain Res.*, **8**: 335-342, 1983.
43. PETTOROSSI, V. E., DELLA TORRE, G., GRASSI, S., ERRICO, P. and ZAMPOLINI, M. Role of NMDA receptors in oculomotor plasticity. *Neurosci. Lett.*, Suppl., **39**: 169, 1990.
44. POMPEIANO, O. and ALLUM, J. H. J. (Eds.) *Vestibulospinal Control of Posture and Movement*. Progr. in Brain Res., Vol. 76. Amsterdam, Elsevier, 1988.
45. PRECHT, W. and DIERINGER, N. Neuronal events paralleling functional recovery (compensation) following peripheral vestibular lesions. pp. 251-268. In: BERTHOZ, A. and MELVILLE JONES, G. (Eds.), *Adaptive Mechanisms in Gaze Control. Facts and Theories*. Amsterdam, Elsevier, 1985.
46. PUTKONEN, P. T. S., COURJON, J. H. and JEANNEROD, M. Compensation of postural effects of hemilabyrinthectomy in the cat. A sensory substitution process? *Exp. Brain Res.*, **28**: 249-257, 1977.
47. RAUSCHECKER, J. P. Mechanisms of visual plasticity: Hebb synapses, NMDA receptors, and beyond. *Physiol. Rev.*, **71**: 587-615, 1991.
48. RAYMOND, J., DEMEMES, D. and NIEOULLON, A. Neurotransmitters in vestibular pathways. Pp. 29-43. In POMPEIANO, O. and ALLUM, J. H. J. (Eds.), *Vestibulospinal Control of Posture and Movement*. Progr. in Brain Res., Vol. 76. Amsterdam, Elsevier, 1988.
49. RAYMOND, J., TOUATI, J. and DEMEMES, D. Changes in glutamate binding sites in the rat vestibular nuclei following hemilabyrinthectomy. *Soc. Neurosci., Abstr.*, **15**: 518, 1989.
50. SANSOM, A. J., DARLINGTON, C. L. and SMITH, P. F. Intraventricular injection of an NMDA antagonist disrupts vestibular compensation. *Neuropharmacol.*, **29**: 83-84, 1990.
51. SCHAEFER, K. P. and MEYER, D. L. Compensation of vestibular lesions. Pp. 463-490. In: KORNHUBER, H. H. (Ed.), *Vestibular System. Handbook of Sensory Physiology*, Vol. VI/2, Berlin, New York, Springer, 1974.
52. SCHMIDT, J. T. Long-term potentiation and activity-dependent retinotopic sharpening in the regenerating retinotectal projection of goldfish: common sensitive period and sensitivity to NMDA blockers. *J. Neurosci*, **10**: 233-246, 1990.
53. SCHMIDT, R. and LAPP, H. Regional distribution of ependymins in goldfish brain measured by radioimmunoassay. *Neurochem. Int.*, **10**: 383-390, 1987.
54. SMITH, P. F. and DARLINGTON, C. L. The NMDA antagonists MK801 and CPP disrupt compensation for unilateral labyrinthectomy in the guinea pig. *Neurosci. Lett.*, **94**: 309-313, 1988.
55. SMITH, P. F. and CURTHOYS, I. F. Mechanisms of recovery following unilateral labyrinthectomy: a review. *Brain Res. Rev.*, **14**: 155-180, 1989.
56. SMITH, P. F. and DARLINGTON, C. L. Neurochemical mechanisms of recovery from peripheral vestibular lesions (vestibular compensation). *Brain Res. Rev.*, **16**: 117-133, 1991.
57. SPRINGER, A. D., EASTER, S. S. and AGRANOFF, B. W. The role of optic tectum

in various visually mediated behaviors in goldfish. *Brain Res.*, **128**: 393-404, 1977.
58. STAUBLI, U. and LYNCH, G. NMDA receptors and memory: evidence for pharmacological and correlational studies. Pp. 129-148. In KOZIKOWSKI, A. P. and BARRIONUEVO, G. (Eds.), *Neurobiology of the NMDA Receptor*. Weinheim, New York, Cambridge, VCH, 1991.
59. WATKINS, J. C. and COLLINGRIDGE, G. L. (Eds.) *The NMDA Receptor*. Oxford, Oxford University Press, 1989.
60. WILL, U., KORTMANN, H. and FLOHR, H. HRP study on structural changes in the commissural fiber system of Rana temporaria following labyrinthectomy. Pp. 345-355. In: FLOHR, H. (Ed.), *Post-Lesion Neural Plasticity*. Berlin, Heidelberg, New York, Springer, 1988.
61. XERRI, C., LACOUR, M. and BOREL, L. Multimodal sensory substitution process in vestibular compensation. Pp. 357-370. In: FLOHR, H. (Ed.), *Post-Lesion Neural Plasticity*. Berlin, Heidelberg, New York, Springer, 1988.
62. XERRI, C. and ZENNOU, Y. Sensory, functional and behavioral substitution processes in vestibular compensation. pp. 35-58. In: LACOUR, M., TOUPET, M., DENISE, P. and CHRISTEN, Y. (Eds.), *Vestibular Compensation. Facts, Theories and Clinical Perspectives*. Amsterdam, Elsevier, 1989.