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Molecular Mechanisms of Brainstem Plasticity

The Vestibular Compensation Model

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Contents

Abstract

Vestibular compensation is the process of behavioral recovery that occurs following unilateral deafferentation of the vestibular nerve fibers (unilateral labyrinthectomy, UL). Since UL results in a permanent loss of vestibular input from the ipsilateral vestibular (VIIIth) nerve, vestibular compensation is attributed to CNS plasticity and has been used as a general model of lesion-induced CNS plasticity. Behavioral recovery from the ocular motor and postural symptoms of UL is correlated with a partial return of resting activity to neurons in the vestibular nucleus (VN) on the deafferented side (the "deafferented VN"), and lesions to the deafferented VN prevent compensation; therefore, the regeneration of resting activity within the deafferented VN is believed to have a causal role in vestibular compensation. The biochemical mechanisms responsible for the adaptive neuronal changes within the deafferented VN are poorly understood. Neuropeptide hormone fragments, such as

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adrenocorticotrophic hormone (ACTH)-4-10, have been shown to accelerate vestibular compensation and can act directly on some VN neurons in vitro. Antagonists for the *N*-methyl-D-aspartate (NMDA) receptor have been shown to inhibit vestibular compensation if administered early in the compensation process. Biochemical studies in frog indicate marked alterations in the phosphorylation patterns of several proteins during compensation, and the in vitro phosphorylation of some of these proteins is modulated by ACTH-(1-24), calcium (Ca^{2+}), and calmodulin or protein kinase C. It is therefore possible that ACTH fragments and NMDA antagonists (via their effects on NMDA receptor-mediated Ca^{2+} channels) modulate vestibular compensation through their action on Ca^{2+}-dependent pathways within VN neurons. Recent studies have shown that some Ca^{2+} channel antagonists and the Ca^{2+}-dependent enzyme inhibitor calmidazolium chloride facilitate vestibular compensation. How the regulation of Ca^{2+} may be related to the neuronal changes responsible for vestibular compensation is unclear at present.

Index Entries: Phosphorylation; neuropeptides; calcium; lesion-induced plasticity; vestibular compensation.

Introduction

Major advances have been made in understanding the neurochemical bases of neural plasticity in the limbic system and neocortex, for example, long-term potentiation in the hippocampus (e.g., Linden et al., 1988), kindling in the septum and amygdala (e.g., Wu et al., 1990), and monocular deprivation plasticity in the visual cortex (e.g., *see* Collingridge and Singer, 1990 for a review). Although plasticity in the hindbrain and spinal cord has received less attention, many areas of the cerebellum (e.g., Ito, 1982), brainstem (e.g., Lisberger, 1988), and spinal cord (e.g., Wolpaw et al., 1983) have also been shown to possess an extensive capacity for plasticity under conditions of altered synaptic input. Vestibular compensation, the gradual recovery of ocular motor and postural behavior that results from the loss of input from one vestibular (VIIIth) nerve, is one example of brainstem plasticity that has been used as a model for studying lesion-induced plasticity in the CNS (*see* Precht and Dieringer, 1985; Flohr et al., 1989; Smith and Curthoys, 1989 for reviews).

The Vestibular Compensation Model

Models of lesion-induced plasticity require a specific, reproducible lesion and a well-defined measure of the effect of the lesion, preferably one that can be quantified on both behavioral and neural levels (*see* Darlington and Smith, 1991a, for a review). The vestibular compensation model fulfills both of these requirements. The lesion itself, accomplished by unilateral surgical labyrinthectomy (UL) or VIIIth nerve section, is isolated in the peripheral nervous system and results in partial deafferentation of the vestibular nuclei (VN) on the side of the brainstem ipsilateral to the UL. The loss of excitatory input from the ipsilateral vestibular nerve causes a loss of resting activity and response to head movement in many neurons in the VN on the deafferented side (the "deafferented VN"), resulting in an imbalance in neural activity between the VN on each side of the brainstem. Because many VN neurons project directly to the motoneurons controlling the ocular and skeletal musculature (*see* Wilson and Melvill Jones, 1979 for a review), the imbalance in neural activity caused by UL generates a characteristic syndrome of ocular motor and postural symptoms that is consistent within species and similar between species as diverse as tadpole and human (*see* Smith and Curthoys, 1989 for a review). These symptoms fall into two categories: *Static symptoms*, which persist in the absence of head movement (e.g., eye deviation, spontaneous ocular nystagmus, yaw head tilt, and roll head tilt); and *dynamic symptoms*, which occur as a result of head movement (e.g., impaired gain and phase of the vestibulo-ocular and vestibulo-spinal reflexes) (Fisch, 1973; Maioli et al., 1983).

Vestibular compensation is the process of behavioral recovery in which many of the symptoms of UL disappear or are reduced in severity over time. However, the precise time-course of vestibular compensation varies among species, and among different ocular motor and postural symptoms. The compensation of the static ocular motor and postural symptoms is correlated with the partial return of resting activity to neurons in the deafferented VN, i.e., the partial rebalancing of activity between the VN on the two sides of the brainstem (*see* Figs. 1 and 2). 2-Deoxyglucose studies have demonstrated a recovery toward more symmetrical metabolic activity between the bilateral VN, with the greater symmetry being between the bilateral medial VN (MVN) (Llinas and Walton, 1979; Flohr et al., 1981; Luyten et al., 1986; Maeda, 1988). Electrophysiological studies in mammals have shown that the recovery of resting activity on the deafferented side is particularly pronounced in the MVN (Precht et al., 1966; McCabe and Ryu, 1969; McCabe et al., 1972; Ried et al., 1984; Hamann and Lannou, 1988; Smith and Curthoys, 1988a; de Waele et al., 1988; Newlands and Perachio, 1990) and occurs to a lesser extent in the lateral VN (Xerri et al., 1983; Pompeiano et al., 1984). In guinea pig, compensation of the static symptoms (Smith et al., 1986a; de Waele et al., 1989a) and recovery of resting activity in the deafferented MVN occur within approx 2 d postUL (Smith and Curthoys, 1988a, de Waele et al., 1988) (*see* Fig. 1 B and Fig. 2). In the frog, compensation of the static postural symptoms occurs over a longer time-course, approx 40–70 d postUL (Flohr et al., 1981), and also correlates with a return of resting activity to neurons in the deafferented VN (Dieringer and Precht, 1979) (*see* Fig. 1 A). Since there is no return of resting activity to the remaining portion of the deafferented vestibular nerve (Sirkin et al., 1984; Jensen, 1983; Smith and Curthoys, 1988a), and since the vestibular nerve does not successfully regenerate (Igarashi et al., 1970; Schuknecht, 1982), the return of resting activity to the deafferented VN must be owing to plastic changes within the CNS.

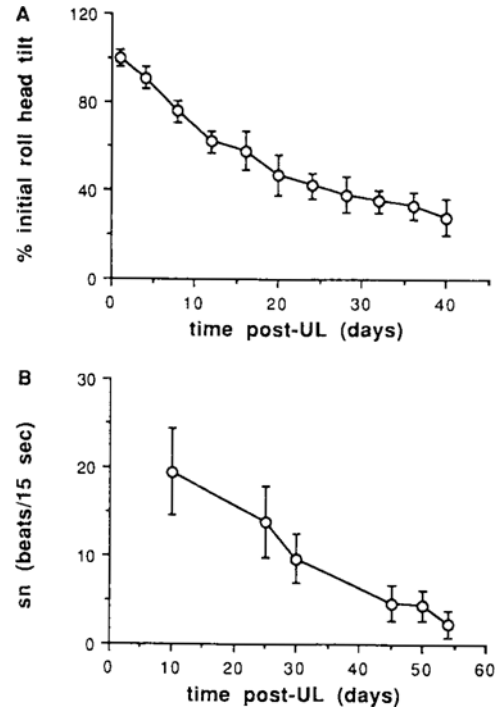

Fig. 1. A: Compensation of roll head tilt following unilateral labyrinthectomy (UL) in frog. The data are expressed as percentages of the initial roll head tilt value. Circles represent mean roll head tilt (n = 261); bars represent 1 SD. Modified from Luneburg and Flohr (1988). B: Compensation of spontaneous ocular nystagmus (sn) following UL in guinea pig. The data are expressed as frequency of quick phase beats/15-s interval. Circles represent means (n = 7); bars represent 1 SD.

The regeneration of resting activity within the deafferented VN is believed to have a causal role in the vestibular compensation process, since lesions of the VN prevent static compensation (Spiegel and Demetriades, 1925). In such species as the frog, vestibular compensation is associated with an increase in the efficacy of brainstem commissural inputs to the deafferented VN from the contralateral VN (Dieringer and Precht, 1977), and transection of the brainstem commissures causes decompensation (Bienhold and Flohr, 1978). However, in mammalian species, transection of the brainstem vestibular commissures does not produce

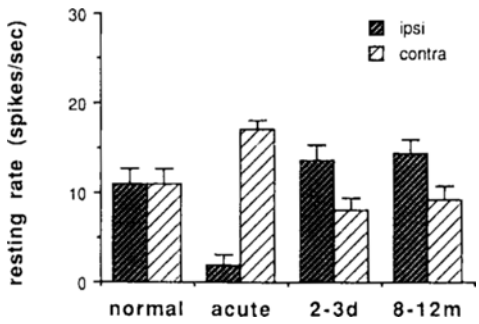

Fig. 2. Resting activity of type I neurons in the medial vestibular nucleus (MVN) of the guinea pig before, and at various stages following, unilateral labyrinthectomy (UL). Histograms represent mean resting activity for single neurons in the different conditions; bars represent 1 SEM; ipsi: MVN ipsilateral to the UL; contra: MVN contralateral to the UL; normal: labyrinthine-intact condition; note that in this case, the same data are shown for ipsi and contra; acute: 0–8 h postUL; 2–3d: 52–60 h postUL; 8–12m: 8–12 mo postUL. These data are based on recordings from 897 neurons. Modified from Smith and Curthoys (1988a,b).

decompensation (Smith et al., 1986b; Newlands and Perachio, 1986, 1987; however, *see* Maeda, 1988) nor does it reduce the level of the regenerated resting activity in the deafferented MVN (Precht et al., 1966; Smith and Curthoys, 1988a). The latter evidence suggests that in mammals, compensation of the static symptoms of UL is independent of commissural input from the contralateral VN.

The dynamic symptoms of UL include a disruption of the vestibularly mediated ocular motor and postural reflexes, which are elicited by head movement. The dynamic symptoms compensate much more slowly and incompletely than the static symptoms (e.g., Halmagyi et al., 1990), and consistent with this result, there appears to be only a limited recovery of response to head movement in the VN (*see* Smith and Curthoys. 1989 for a review). Because the extent of the compensation of the dynamic symptoms is questionable, we have focused on the static symptoms of UL and the recovery of resting activity in the deafferented VN with which it correlates.

Physiological Basis of Vestibular Compensation

It is unclear whether the mechanisms of the regeneration of resting activity and the other neuronal changes that may be occurring in the deafferented VN have a pre- or a postsynaptic locus, or both. Presynaptic changes, such as substitution of nonvestibular sensory inputs and reactive synaptogenesis, have been suggested, as have postsynaptic changes, such as upregulation of excitatory postsynaptic receptors (e.g., glutamatergic denervation supersensitivity) or amplification of intrinsic membrane properties (e.g., L-type voltage-sensitive Ca^{2+} channels) (*see* Precht and Dieringer, 1985; Smith and Curthoys, 1989; Flohr et al., 1989; de Waele et al., 1989b; Smith and Darlington, 1991 for reviews). To date, experimental evidence does not clearly support any of these hypotheses as an explanation of vestibular compensation in all species. Although disruption of nonvestibular sensory inputs has been shown to alter the time-course of vestibular compensation, in most studies, compensation still occurs; although there is evidence for reactive synaptogenesis in the frog, there is little evidence to support its occurrence in mammals, and in any case, only very rapid forms of dendritic modification could account for the rapid time-course of static compensation in mammalian species; neither behavioral nor neurotransmitter binding studies clearly support the denervation supersensitivity hypothesis (*see* Flohr et al., 1985; 1989; Smith and Curthoys, 1989; Smith and Darlington, 1991 for reviews). Recent studies in the squirrel monkey suggest that glutamate levels in the deafferented VN may change during vestibular compensation; therefore presynaptic changes may be involved (Henley and Igarashi, 1991).

It has been suggested that an intrinsic capacity of the cell membrane for repetitive firing may underlie the regeneration of resting activity that occurs in the lateral cuneate nucleus following partial deafferentation (Kjerulf and Loeser, 1973). Such a mechanism may also be operating in the

deafferented VN, since recent studies have demonstrated that MVN neurons in vitro exhibit resting activity in the absence of synaptic input (Darlington et al., 1989,1990; Lewis et al., 1989; Smith et al.,1991; Serafin et al., 1990,1991 a,b) and have intrinsic membrane properties, such as persistent Na^+ conductances and low (i.e., T-type) and high (i.e., L-type) threshold Ca^{2+} conductances (Serafin et al., 1990,1991 a,b).

Possible Neurochemical Mechanisms

Two prominent lines of research in other areas of neural plasticity have been the effects of adrenocorticotrophic hormone (ACTH)-related neuropeptides on lesion-induced plasticity in the central and peripheral nervous systems (*see* Strand et al., 1989 for a review) and the contribution of the *N*-methyl-D aspartate (NMDA) receptor to long-term potentiation (e.g., *see* Collingridge and Bliss, 1987 for a review). There is also evidence to suggest that ACTH-related neuropeptides and the NMDA receptor may be involved in the mechanisms of vestibular compensation (*see* Flohr et al., 1989; Darlington and Smith, 1991; Smith and Darlington, 1991 for reviews).

The effects of neuropeptides on vestibular compensation were first reported in the early 1980s. Flohr and Luneburg (1982) reported that ACTH-(4-10) was effective in enhancing the compensation of roll head tilt in frogs (Fig. 3A). Further investigations indicated that ACTH-(1-10), the ACTH-(4-9) analog ORG-2766, and α-MSH all accelerated vestibular compensation, whereas ACTH—(1-39), (1-24), (4-6), and (5-7) were ineffective (Luneburg and Flohr, 1988; Flohr and Luneburg, 1989), and hypophysectomy retarded the compensation process (Flohr and Luneburg, 1982). These results suggested that the 4-9 fragment of the ACTH molecule contains the critical elements for enhancing compensation. Administration of (D-Phe^7) ACTH-(4-10), in which the phenylalanine residue in the seventh-position is altered to the D form, increased the magnitude of the roll head tilt and retarded the development of compensation (*see* Fig. 3A). (D-Phe^7) ACTH-(4-10) caused decompensation in partially compensated frogs (Luneburg and Flohr, 1988).

In mammals, only the effects of ACTH-(4-10) and (D-Phe^7) ACTH-(4-10) have so far been investigated. Compensation of spontaneous nystagmus was enhanced in squirrel monkey by treatment with ACTH-(4-10) (Igarashi et al., 1985,1988; Ishii and Igarashi, 1987). In guinea pig, the compensation of spontaneous nystagmus was accelerated by treatment with ACTH-(4-10) (*see* Fig. 3B), whereas postural compensation was unaffected (Gilchrist et al., 1990, in press). Treatment with (D-Phe^7) ACTH-(4-10) increased the levels of spontaneous nystagmus throughout compensation (Gilchrist et al., in press) (*see* Fig. 3B). The increase in UL symptoms, in both frog and guinea pig, following administration of (D-Phe^7) ACTH-(4-10), suggests that there may be an endogenous ACTH-(4-10) that is important to the compensation process. We have recently shown that ACTH-(4-10) can act directly on MVN neurons in brainstem slices (Darlington et al., 1990) (*see* Fig. 4); however, how this action may be related to vestibular compensation is currently unknown.

The first research on the NMDA receptor in relation to vestibular compensation was reported by Cochran et al. (1987) and Knopfel and Dieringer (1988) using brainstem explants removed from compensated frogs. These authors were unable to find any evidence to suggest that NMDA receptors contribute to the increased efficacy of brainstem commissural inputs to the deafferented VN in frogs at 6 wk to 1 y postUL. The authors concluded that NMDA receptors were not involved in the mechanism of vestibular compensation in frogs. Recently, however, Luneburg and Flohr (1990) have demonstrated that a single injection of the noncompetitive NMDA antagonist, MK801, administered within the first 6 wk postUL, retarded vestibular compensation in frogs (*see* Fig. 5A). This result suggests that the NMDA receptor may contribute

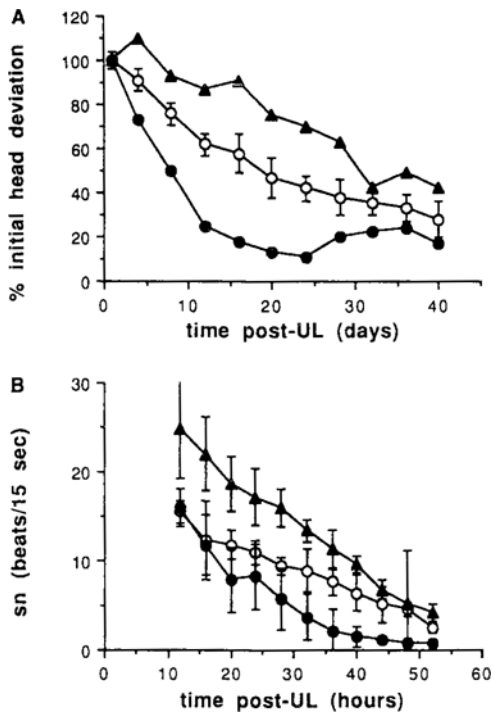

Fig. 3. Effect of ACTH-(4-10) and [D-Phe^7] ACTH-(4-10) on the compensation of roll head tilt and spontaneous nystagmus following unilateral labyrinthectomy (UL) in the frog and guinea pig (respectively). Symbols represent mean values. **A.** Control: daily intralymphatic (il) injections of frog Ringer (17 mL/kg), from 1–24 d postUL (n = 261). ACTH-(4-10): daily il injections of ACTH-(4-10) (300 nmol/kg), from 1–24 d postUL (n = 35). [D-Phe7] ACTH-(4-10): daily il injections of [D-Phe^7] ACTH-(4-10) (1200 nmol/kg), from 1–31 d postUL (n = 34). Modified from Luneburg and Flohr (1988). —○— Control; —●— ACTH-(4-10); —▲— [D-Phe7]. **B.** Control: im injections of saline (0.1 mL/kg) every 4 h for 48 h postUL (n = 4). ACTH-(4-10): 200 µg/kg i.m ACTH-(4-10) every 4 h for 48 h postUL (n = 4). [D-Phe7] ACTH-(4-10): 800 µg/kg [D-Phe7] ACTH-(4-10) i.m every 4 h for 48 h postUL (n = 4). Modified from Gilchrist et al. (1990; in press).

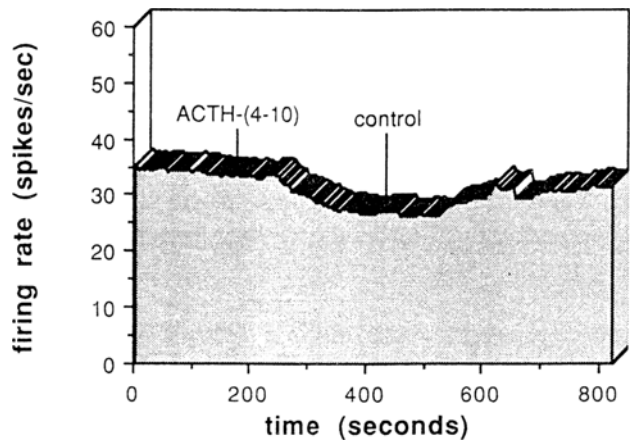

Fig. 4. Effect of $10^{-14}M$ ACTH-(4-10) on a single medial vestibular nucleus neuron in a brainstem slice from a labyrinthine-intact guinea pig. Points represent successive 2 sec bins of averaged resting activity. "ACTH" indicates the onset of the artificial cerebrospinal fluid (ACSF) containing the ACTH-(4-10). "C" indicates the offset of the ACTH-(4-10) solution and the onset of the control ACSF solution. Modified from Darlington et al. (1990).

to the compensation process in frogs, but that there may be a critical period for this contribution. In guinea pig, NMDA receptor antagonists, administered systemically or directly into the deafferented VN via a cannula, have also been demonstrated to disrupt the development of vestibular compensation if administered before compensation is complete (Darlington and Smith, 1989; Sansom et al., unpublished observations) and to cause decompensation if administered between 2–7 d postUL (Smith and Darlington, 1988; Sansom et al., 1990; Pettorossi et al., 1990; de Waele et al., 1990) (*see* Fig. 5B). However, consistent with the results of Luneburg and Flohr (1990), suggesting a critical period for the administration of NMDA antagonists in the frog, administration of NMDA antagonists from 14 d up to 3 mo postUL had little effect on either ocular motor or postural compensation (Darlington and Smith, 1989).

It is possible that vestibular compensation occurs in a series of stages, for example, development stages followed by maintenance stages, and that the NMDA receptor is important during the development of compensation, whereas other processes are important for its long-term maintenance (Darlington and Smith, 1989; Smith and Darlington, 1991; Luneburg and Flohr, 1990). This seems a worthwhile hypothesis given that NMDA receptors are involved in the induction, but not the maintenance, of long-term poten-

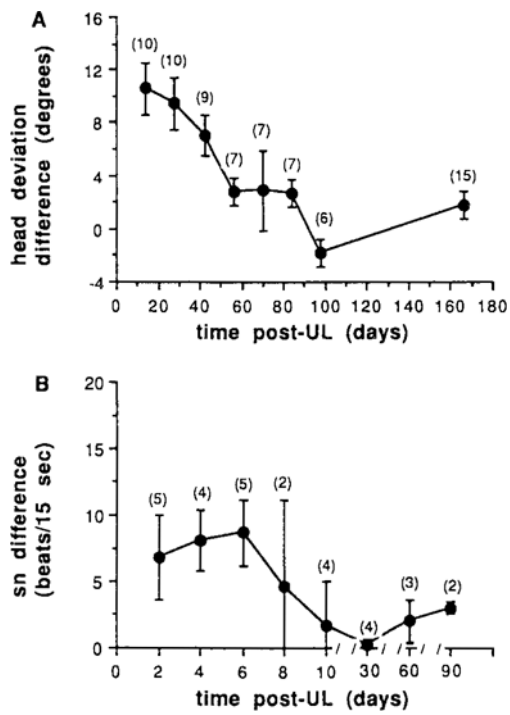

Fig. 5. A. Difference in roll head tilt to the side of the unilateral labyrinthectomy (UL) before and 24 h after a single injection (2.0 mg/kg il) of MK801 in frog. Circles represent means; bars represent 1 SEM. Modified from Luneburg and Flohr (1990) B. Difference in sn before and within 2 h following a single injection of MK801 (1.0 mg/kg im) in guinea pig. Circles represent means; bars represent 1 SD. Modified from Darlington and Smith (1989). The numbers in brackets indicate the number of animals at each time.

tiation (*see* Collingridge and Bliss, 1987 for a review). Recent studies suggest that there may be an interaction between NMDA receptors and ACTH release (Iyengar et al., 1990).

Molecular Mechanisms

The first indications of the types of molecular mechanisms that may underlie vestibular compensation have come from recent biochemical studies that have examined changes in phosphorylation patterns associated with vestibular compensation. Given that the process of vestibular compensation begins immediately following UL and that, at least in mammals, the major part of static compensation is complete within 2–3 d postUL, modification of existing protein seems a probable molecular substrate for the physiological changes that underlie the behavioral recovery.

Using whole brain homogenates from frogs at different stages of compensation, Flohr et al. (1985) have demonstrated that a number of phosphoproteins are affected during the compensation process, with two particularly interesting changes occurring at 1–3 d and 7–14 d postUL. At 1–3 d, there was an increase in a 21-kDa phosphoprotein. The phosphorylation of this protein appeared to be independent of cyclic adenosine-3',5'-monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), but modulated by calcium (Ca^{2+}) (Flohr et al., 1985), calmodulin (Janssen et al., 1987), and ACTH-(1-24) (Flohr et al., 1985). By 7–14 d postUL, a 48-kDa phosphoprotein was markedly increased. Phosphorylation of this protein was modulated by protein kinase C (Janssen et al., 1988,1989). These results suggest a role for intracellular Ca^{2+} in the vestibular compensation process.

If intracellular Ca^{2+} is involved in the mechanisms of compensation, then administration of drugs that manipulate intracellular Ca^{2+} pathways would be expected to affect the time-course of compensation. Recently, this hypothesis has been examined using behavioral studies in frogs and guinea pigs.

Preliminary results from frogs suggest that administration of the T-type Ca^{2+}-channel antagonist flunarizine (Takahashi and Akaike, 1991) enhances the compensation of roll head tilt (Leinhos and Flohr, personal communication). In guinea pig, Tolu et al. (1988a,b) have reported that administration of flunarizine significantly accelerated the compensation of the postural and ocular motor symptoms observed following UL, and that by 24 h postUL, spontaneous nystagmus had disappeared. Tolu et al. also reported that systemic administration of flunarizine resulted in a decrease in the resting activity of VN neurons following compensation for a bilateral labyrinthectomy.

To further study the contribution of Ca^{2+}-dependent processes in vestibular compensation, we have conducted a series of experiments examining the effects of the L-type Ca^{2+} channel antagonist verapamil (Frank, 1986; Zernig, 1990) and the Ca^{2+}-dependent enzyme inhibitor calmidazolium chloride (R 24571) on the compensation of spontaneous nystagmus (SN) in guinea pig. Three or more injections of verapamil during the first 24 h postUL had little effect on the compensation of SN relative to control animals; however, a single injection of verapamil 1 h before UL resulted in an acceleration of SN compensation (Darlington and Smith, 1991b) (*see* Fig. 6). Calmidazolium chloride was administered by intraventricular injection to guinea pigs following UL and caused a dramatic decrease in the amount of SN observed in the experimental animals at 10 h postUL, compared to control animals (Fig. 7). However, by 25 h postUL, SN had returned to the level observed in the control animals (Sansom et al., in preparation). In animals that received the calmidazolium injections, postural symptoms, such as yaw and roll head tilt, were also less severe during the first 10 h postUL; however, the severity of these symptoms did not return to control levels later in the compensation process.

How flunarizine, verapamil, and calmidazolium chloride may be acting to modulate the time-course of vestibular compensation is unknown. Although flunarizine is currently believed to act on T-type Ca^{2+} channels (Takahashi and Akaike, 1991) and verapamil is known to act on L-type Ca^{2+} channels (Frank, 1986), the extent to which the various organic Ca^{2+} channel antagonists are selective for specific Ca^{2+} channel subtypes is still unclear, and some drugs, such as verapamil, are known also to affect Na^{+} channels and GABA and dopamine release (Sitges et al., 1990). There is also reason to question the selectivity of the action of calmidazolium chloride. Although calmidazolium chloride is known to act as a calmodulin antagonist (Mazzei et al., 1984; Thayer and Fairhurst, 1983), it has also been shown to inhibit with equal potency protein

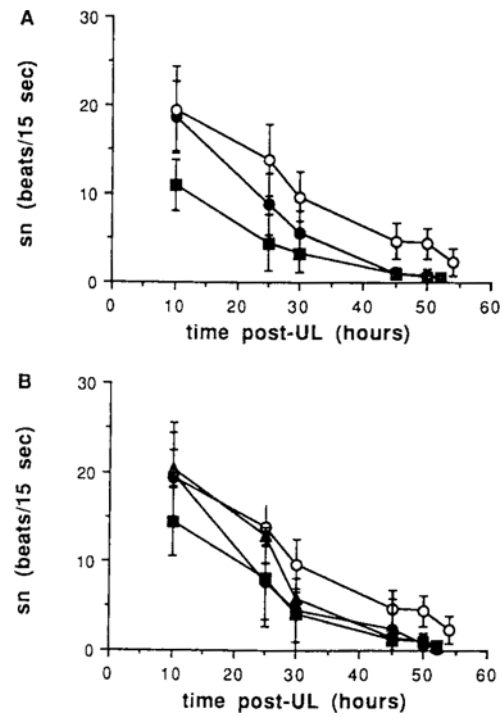

Fig. 6. Effect of im injections of verapamil on the compensation of spontaneous nystagmus (sn) following unilateral labyrinthectomy in guinea pig. Control: animals receiving no injection (n = 7). A:–1 h: animals receiving a single 0.4 (n = 4) or 0.8 mg/kg (n = 3) im injection of verapamil 1 h before UL.—○— Control; —●— –1 h (0.4 mg/kg_; —■— – 1 h (0.8 mg/kg). B: 0–24 H: animals receiving 0.2 mg/kg im injections of verapamil, every 4 h for 24 h postUL (n = 4). 0–8 h: animals receiving 0.2 (n = 4) or 0.4 (n = 4) mg/kg im injections of verapamil, every 4 h for 8 h postUL. Symbols represent means; bars represent 1 SD (Darlington and Smith, in preparation). —○— Control; —●— 0–24 h (0.2 mg/kg); —■— 0–8 h (0.2 mg/kg); —▲— 0–8 h (0.4 mg/kg).

kinase C (Mazzei et al., 1984). In addition, it has been demonstrated to inhibit calmodulin-dependent Ca^{2+}-ATPase and the calmodulin-regulated enzymes, brain phosphodiesterase and phosphorylase b kinase (Van Belle, 1981). A recent in vitro study using isolated molluscan nerve cells has shown that extracellular application of calmidazolium chloride has a dose-dependent effect on the inward current of voltage-dependent Ca^{2+} channels (Doroshenko et al., 1988). Whether the

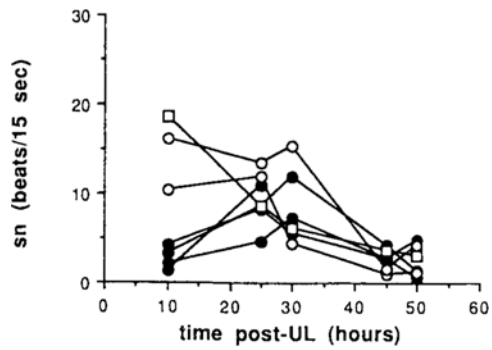

Fig. 7. Effect of intraventricular (ivt) injections of calmidazolium chloride (R 24571) on spontaneous nystagmus (sn) following unilateral labyrinthectomy (UL) in guinea pig. R 24571: Each animal (n = 4) received an ivt injection of R 24571 (0.5 mM, dissolved in 1 µL of artificial cerebrospinal fluid [ACSF] and dimethyl sulfoxide [DMSO], pH approx 7.0) at 0.5, 2.5, and 4.5 h postUL. DMSO control: similar injections of DMSO alone (n = 2). ACSF control: similar injections of ACSF alone (n = 1). Mean sn values for the individual animals are shown. Modified from Sansom et al. (in preparation). —●— R24571; —○— DMSO control; —□— ACSF control.

effects on vestibular compensation produced by calmidazolium chloride are related to calmodulin, protein kinase C, or some other Ca^{2+}-related process cannot be determined from the present results. However, since the phosphorylation changes at 1 d postUL in the frog are related to calmodulin (Janssen et al., 1987), it may be that calmodulin is also involved in the mechanism of compensation of SN in guinea pig, during the first 2 d postUL.

It is possible that Ca^{2+} channel antagonists and calmidazolium chloride facilitate compensation simply by reducing activity within the VN contralateral to the UL, so that its resting activity balances at a lower level with the hypoactive VN on the ipsilateral side. This seems an unlikely explanation for two reasons. First, a single injection of verapamil 1 h before UL resulted in a lower than normal SN frequency even at 25 h postUL (*see* Fig. 6); given that verapamil has a half-life of approx 5 h (*see* Needleman et al., 1985 for a review), it seems unlikely that it could reduce SN frequency at 25 h postUL merely by suppressing resting activity in the contralateral VN. Secondly, suppression of activity in the contralateral VN, while the ipsilateral VN is also hypoactive, would be expected to disrupt vestibular nystagmus evoked by head movement; this deficit was not observed. Since Ca^{2+} antagonists have been reported to facilitate recovery in cases of CNS damage (Finger et al., 1990; Pohorecki et al., 1990), another possibility is that Ca^{2+} antagonists facilitate vestibular compensation by reducing excitotoxicity caused by an excessive Ca^{2+} influx following deafferentation of the VIIIth nerve (Darlington and Smith, 1991b, in preparation). At present, there is no direct evidence to support this hypothesis in relation to vestibular compensation.

Conclusions

As a model of lesion-induced CNS plasticity, vestibular compensation offers the unique advantage that physiological and biochemical research can be related to behavioral studies of well-defined reflex pathways. As a result, electrophysiological changes within the deafferented VN have been correlated with the time-course of compensation of UL symptoms, such as spontaneous nystagmus and yaw and roll head tilt. However, despite the numerous behavioral and electrophysiological studies, the biochemical mechanisms of vestibular compensation are still poorly understood. Evidence from frog (Flohr and Luneburg, 1982), guinea pig (Gilchrist et al., 1990), and squirrel monkey (Igarashi et al., 1985) indicates that compensation can be accelerated by neuropeptide fragments, such as ACTH-(4-10), and recent in vitro results suggest that ACTH-(4-10) may act directly on some VN neurons (Darlington et al., 1990). The phosphorylation of a 21-kDa protein, which is enhanced at 1–3 d postUL in frogs, can be modulated not only by ACTH-(1-24), but also by Ca^{2+} and calmodulin (Flohr et al., 1985; Janssen et al., 1987); therefore, it is possible that ACTH-(4-10) exerts its effects on vestibular compensation via Ca^{2+}-dependent

pathways (Flohr et al., 1985). Results from guinea pig (e.g., Smith and Darlington, 1988) and frog (Luneburg and Flohr, 1990) suggest that NMDA receptors may also be involved in an early phase of the compensation process. The Ca^{2+} influx that results from NMDA receptor activation is an important intracellular signal in the induction of long-term potentiation (*see* Collingridge and Bliss, 1987 for a review) and it is possible that NMDA receptor-mediated Ca^{2+} influx has a similar role in vestibular compensation. Recent behavioral studies in guinea pig (Tolu et al., 1988a,b; Darlington and Smith, 1991b, in preparation; Darlington et al., in preparation) and frog (Lienhos and Flohr, personal communication) have directly addressed the possible contribution of Ca^{2+}-dependent processes to vestibular compensation: Ca^{2+} channel antagonists, such as flunarizine and verapamil, have been shown to accelerate compensation, and the Ca^{2+}-dependent enzyme inhibitor calmidazolium chloride has been shown to reduce ocular motor and postural symptoms during the first 10 h postUL. Although, so far, most studies have used systemic administration of Ca^{2+}-modulating drugs, it is conceivable that their effects are owing to action within the VN, since in vitro electrophysiological studies have shown that VN neurons have both NMDA receptor-mediated Ca^{2+} channels (e.g., Cochran et al., 1987) and L- and T-type voltage-sensitive Ca^{2+} channels (Serafin et al., 1990, 1991a,b). At present, the precise relationship between Ca^{2+}-dependent processes and the neuronal changes within the deafferented VN that are responsible for vestibular compensation is unknown. However, on present evidence, it seems likely that Ca^{2+}-dependent phosphorylation may be part of the molecular mechanism of vestibular compensation.

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