

# THE VESTIBULO-OCULAR AND THE VESTIBULOSPINAL REFLEXES: NORADRENERGIC INFLUENCES ON THE PLASTIC CHANGES WHICH AFFECT THE CEREBELLAR CORTEX DURING VESTIBULAR ADAPTATION

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## SECTION 1. INHIBITORY INFLUENCE OF CEREBELLAR PURKINJE (P-) CELLS ON THEIR TARGET NEURONS

The inhibitory influence that P-cells of the cerebellar cortex exert on their target neurons was originally proposed after the demonstration that stimulation of the cerebellar anterior vermis exerts an inhibitory influence on posture. Observations made in decerebrate cats had actually shown that the suppression of the postural activity which occurred in the ipsilateral limbs during this vermal stimulation was followed by a rebound effect, characterized by a prominent increase in the decerebrate rigidity which occurred at the end of this stimulation (Sherrington, 1898; Bremer, 1922; Dow and Moruzzi, 1958). This finding led Moruzzi (1950) to postulate the existence of two different populations of cortico-cerebellar units, one being inhibitory, while the other being excitatory in function. These opposite results could be dissociated in two ways. The first was by submitting the vermal cortex of the cerebellar anterior lobe to different frequencies of electrical stimulation. In particular, Moruzzi (1950) found that while the inhibitory influence on posture followed by a rebound effect was obtained during repetitive *high frequency* stimulation of the cerebellar anterior vermis, a *decrease in this frequency* of stimulation, using the same stimulus intensity and pulse duration, produced a facilitatory influence on posture, which was not followed by rebound.

Attempts to identify the inhibitory pathway, which originated from the cerebellar anterior vermis, thus suppressing the postural activity on the ipsilateral limbs, were first performed by Moruzzi and Pompeiano (1957), who studied the effects of small electrolytic lesions located within or close to the rostral part of the fastigial nucleus on this inhibitory influence. In interpreting their findings, these Authors were aided by the results of the experimental anatomical study made by Walberg and Jansen (1961), who used the method of degenerating fibers to follow the course and the termination of the vermal cerebellar corticovestibular fibers in the cat. These fibers, which originate from the paravermal zone B of the cerebellar anterior vermis, project to the ipsilateral lateral vestibular nucleus (LVN) of Deiters (Corvaja and Pompeiano, 1979; Voogd, 1986), while the corresponding direct cerebellar corticovestibular fibers course through the dorsal aspect of the rostromedial fastigial nucleus (Walberg and Jansen, 1961). A small electrolytic lesion limited to this rostromedial part of the fastigial nucleus, leading to interruption of this pathway, suppressed the inhibitory influence that the cerebellar anterior vermis exerts on decerebrate rigidity (Moruzzi and Pompeiano, 1957, see also Fig 4 in Pompeiano, 1969, 1974). In these experiments, in fact, high frequency repetitive stimulation of the

cerebellar vermis, which in control experiments suppressed the postural activity followed by a rebound effect, now produced a prominent increase in the decerebrate rigidity. The results of this lesion experiment should be integrated by the results of *extracellular unit recording* experiments, showing that in decerebrate cats the discharge of the LVN, as well as of fastigial neurons, could be either inhibited or facilitated by cathodal polarization of the cerebellar anterior vermis (De Vito *et al.*, 1956; Pompeiano and Cotti, 1959; Arduini and Pompeiano, 1957; cf. Brodal *et al.*, 1962).

The hypothesis that this inhibitory influence on the LVN neurons was mediated by the direct cerebellar corticovestibular projection, which would then exert an inhibitory influence on their target neurons, was supported by the fact that this inhibitory influence was somatotopically organized (Pompeiano and Cotti, 1959), following the pattern originally demonstrated in experimental anatomical studies by Brodal *et al.* (1962). In contrast to this finding, the facilitatory effect could be attributed to antidromic activation of cerebellopetal afferents which, through axo-axonal reflex, would lead to activation of excitatory vestibulospinal (VS) and/or fastigial neurons (cf. also Ito, 1984). The inhibitory action that the cerebellar P-cells exert on their target neurons located in the vestibular (and/or cerebellar) nuclei was finally investigated by Ito and Yoshida (1966) and Ito *et al.* (1970), who used experiments of *intracellular recording* to demonstrate that this inhibitory influence was *monosynaptic* in nature. All these observations raised the problem of the important role that the cerebellar cortex exerts on posture as well as on vestibular function.

## SECTION 2. INHIBITORY INFLUENCE OF THE CEREBELLAR ANTERIOR VERMIS ON POSTURE

The demonstration that the P-cells of the cerebellar anterior vermis exert a direct inhibitory influence on the LVN neurons of Deiters, as well as on fastigial neurons, should be associated with the discovery by Lund and Pompeiano (1968), who found that this vestibular structure exerts a direct *monosynaptic* excitatory influence on ipsilateral limb extensor motoneurons (cf. also Pompeiano, 1975). Both these findings indicate that the suppression of postural activity which occurs in decerebrate animals following stimulation of the cerebellar anterior vermis is not due to activation, through the fastigial nucleus, of the inhibitory area of the medullary reticular formation, as originally postulated by Magoun and Rhines (1947), but rather to disfacilitation, i.e. to suppression of the tonic excitatory influence that Deiters' neurons exert on exten-

sor motoneurons (Terzuolo, 1959; Llinás, 1964). In fact, the hyperpolarization of these motoneurons induced by corticocerebellar stimulation could neither be reversed by passing hyperpolarizing current through the membrane of these motoneurons, nor was it associated with the conductance changes which determine the IPSPs after stimulation of the medullary inhibitory region (Jankowska *et al.*, 1964, 1968; Llinás and Terzuolo, 1964).

The demonstration that the P-cells of the cerebellar anterior vermis exert a direct inhibitory influence on Deiters neurons, which in turn exert a monosynaptic excitatory influence on limb and axial extensor motoneurons, indicates the existence of a three-neuronal vestibulospinal reflex (VSR) arc, made by primary vestibular afferents, lateral vestibulospinal (VS) neurons and limb and axial extensor motoneurons, as proposed by Lund and Pompeiano (1968, cf. also Pompeiano, 1975a), in analogy with the three-neuronal vestibulo-ocular reflex arc (VOR) originally described by Lorente de Nó (1933).

However, while the VSR is under the inhibitory control of the zone B of the cerebellar anterior vermis (Corvaja and Pompeiano, 1979, Voogd, 1986), the VOR is under the inhibitory control of the flocculus (cf. Ito, 1982, 1984).

### SECTION 3. INHIBITORY INFLUENCES OF THE CEREBELLAR CORTEX ON: a) THE VESTIBULO-OCULAR REFLEX (VOR), AND b), THE VESTIBULOSPINAL REFLEX (VSR)

It is known that the P-cells of the flocculus project particularly to the medial vestibular nucleus (MVN) and related structures which contribute to the vestibulo-ocular pathway. On the other hand the P-cells of the cerebellar anterior vermis project particularly to the LVN, whose lateral VS axons reach the axial and limb extensor motoneurons (Pompeiano, 1969, 1974, 1975). The similitude in the anatomo-functional organization of the cerebellar control of the VOR with that of the cerebellar influences on the VSR is supported by the results of both electrophysiological and lesion experiments (cf. Ito, 1982, 1984).

#### *a) Cerebellar influences on the VOR*

Observations made by Ito (1982; 1984; Ito *et al.*, 1974) in albino rabbits have shown that most of the flocculus P-cells act out-of-phase with respect to the vestibulo-ocular neurons during sinusoidal rotation about the horizontal plane either of head or of the visual field, thus exerting a positive influence on basic VOR and optokinetic reflex (OKR) gain. This finding was originally supported

by lesion experiments, showing that a bilateral surgical cerebellectomy or flocculectomy produced in albino rabbits a decrease in the simple (non-adapted) gain of the horizontal VOR (the ratio of the amplitude of the compensatory eye movement to the amplitude of the stimulus), and an increase in phase lag of both the horizontal VOR and the horizontal OKR. The reduction of the horizontal VOR gain as described above was in agreement with the results obtained in the chinchilla (Hassul *et al.*, 1976). Moreover, in pigmented rabbits only the OKR gain was reduced after bilateral flocculectomy, while the gain of the VOR remained almost unchanged (Nagao, 1983). These findings were not confirmed by Robinson (1976), who found that a bilateral surgical ablation of the flocculus increased in the cat the gain of the VOR. This finding was contradicted by the results of Keller and Precht (1979), who found that in this animal species total cerebellectomy or flocculectomy reduced the gain of the VOR elicited at relatively low frequency of rotation of the head in light and darkness. The OKR gain was also reduced, but only at high stimulus velocities. Flocculectomy performed in the monkey produced either increase as decrease of the VOR gain in individual subjects (Zee *et al.*, 1981).

The original observation by Ito *et al.* (1974) was finally confirmed by substituting the method of surgical ablation of the flocculus with that of functional inactivation of that corticocerebellar area. Observations made in pigmented rabbits had actually shown that a reversible decrease or depression of the VOR and the OKR occurred after intrafloccular microinjection of a GABA-A (muscimol) or GABA-B (baclofen) agonist (van Neerven, Pompeiano and Collewyn, 1989). Thus, if GABA agonists suppress the modulation of the firing rate of the P-cells by mossy fiber (MF) and climbing fiber (CF) activity, this would lead to a reduced disinhibition of the vestibulo-ocular neurons by floccular P-cells and thus to a decrease in gain of the VOR and OKR. It is important to stress this point, cause simplistic interpretation of the inhibitory nature of the P-cells output has sometimes led to the misunderstanding that the cerebellar side-loop as a whole would have a negative effect on the VOR, thus leading to the expectation that cerebellar lesions or inactivations should result in an enhanced gain of the VOR (Robinson, 1976), although this is contradicted by the vast majority of the literature.

#### *b) Cerebellar influences on the VSR*

In analogy with the VOR which is under the inhibitory control of the flocculus (cf. Ito, 1982, 1984), the VSR is under the inhibitory control of the zone B of the cerebellar anterior vermis (Corvaja and Pompeiano, 1979; Voogd, 1986). In

particular, electrophysiological experiments performed in decerebrate cats have shown that P-cells of the zone B of the cerebellar anterior vermis respond to roll tilt of the whole animal with a modulation of their simple spike discharge (Denoth, Magherini, Pompeiano and Stanojević, 1979, 1980; Bruschini, Andre, Pompeiano and Manzoni, 2006), which is usually opposite in phase with respect to that of the lateral VS neurons (Boyle and Pompeiano, 1980, 1981a, 1981b; Marchand, Manzoni, Pompeiano and Stampacchia, 1987). It appears, therefore, that the contraction of the ipsilateral limb extensors during side-down tilt of the animal depends not only upon an increased activity of the excitatory VS neurons, but also on a reduced discharge of the inhibitory P-cells, leading to disinhibition of the related VS neurons.

The conclusion of these experiments, i.e. that the cerebellar vermis exerts a positive influence on the VSR, was supported by the fact that unilateral microinjection of a GABA-A or GABA-B agonist into the zone B of the cerebellar vermis, leading to inactivation of the corresponding P-cells, decreased the response gain of the ipsilateral triceps brachii to roll tilt of the animal, while just the opposite result occurred after local injection of a GABA-A or GABA-B antagonist (Andre, d'Ascanio, Manzoni and Pompeiano, 1994). The results reported above closely resemble those obtained in intact rabbits on the VOR and the OKR following intrafloccular microinjections of GABA agonists (Van Neerven, Pompeiano and Collewijn, 1989). Inactivation or suppression of the discharge of P-cells of the cerebellar anterior vermis, which particularly acts out-of-phase with respect to that of the VS neurons driven by the same vestibular afferents, would remove one of the main components which contributes to the gain of the VSR, as shown by flocculectomy, which removes or suppresses one of the main components which contributes to the gain of the VOR. Thus, if the GABA agonists suppress the modulation of the firing rate of the P-cells induced by the MF and the CF, this would lead to a reduced disinhibition of the VS neurons by the vermal P-cells, and thus to a decrease in gain of the VSR.

#### SECTION 4. ADAPTATION OF THE VOR DURING COMBINED VISUO-VESTIBULAR STIMULATION AND EFFECTS OF FLOCCULECTOMY

Ito *et al.* (1974) have shown that, in albino rabbits, large and long-lasting changes of the vestibulo-ocular response characteristics could be induced over long periods of combined visual-vestibular stimulation (cf. also Collewijn and Grootendorst, 1978). In particular, they found that sustained oscillation of the

animal in a platform surrounded by an optokinetic stimulus field, which rotates out-of-phase or in phase with the platform, elicited adaptive changes of the horizontal VOR gain, which increased or decreased respectively, depending on the visual stimulus condition combined with the sustained head rotation. Such changes were found to be *adaptive*, in so far as they were appropriate for restoration of reflex retinal image stabilization during head rotation, and they were *plastic* in the sense that, once induced, they persisted some time after. These findings confirm the results of previous observations originally made by Gonshor and Melvill Jones (1971) in humans. Contrary to the variable effects of flocculectomy on the basic gain of the VOR and OKR, in different animal species, all authors agree with Ito's observation (1974, 1979; cf. Ito, 1982, 1984), i.e. that surgical or chemical flocculectomy prevented or severely depressed any adaptive increase in gain of the horizontal VOR (Robinson, 1976; Zee *et al.*, 1981; Nagao, 1983; Lisberger *et al.*, 1984).

Ito also made the additional observation that interruption of the CF input to the flocculus by lesion of the inferior olive (IO) replicated the effects of the flocculectomy (Ito and Migashita, 1975; Haddad *et al.*, 1980). This finding can easily be understood if we consider that the P-cells of the cerebellar flocculus respond not only to primary and secondary vestibular afferents terminating as mossy fibers (MF), but also integrate retinal error signals, which are conveyed in part through climbing fibers (CF). In particular, these fibers were able of modifying the transfer characteristics of MF-parallel fibers across the vestibulocerebellum (Graf *et al.*, 1988), thus leading to the plastic changes which are at the basis of the VOR adaptation. Loss of adaptation of the horizontal VOR gain after IO lesion may thus reflect removal of P-cell influences on relay cells involved in the horizontal VOR. This finding is consistent with the observations that P-cells in the rabbit's flocculus alter their responsiveness to head rotation during adaptation of the horizontal VOR (Dufossé *et al.*, 1978).

#### SECTION 5. FLOCCULUS VERSUS BRAINSTEM HYPOTHESIS OF MOTOR LEARNING IN THE VOR ADAPTATION

Ito's hypothesis (1982) that the flocculus adaptively controls the VOR gain by regulating the signal flow from the labyrinth in the relay cells of the VOR had been challenged by Miles and Lisberger (1981) and Lisberger (1988), who postulate that in monkeys the vestibular nuclei (VN), rather than the cerebellar cortex play an important role in the plastic changes underlying the VOR adaptation.

The two major theories concerning the site (*cerebellar* or *brainstem*) of motor learning were discussed both by Ito and Lisberger and Sernowski (1993), who considered the arguments pro or against the individual hypotheses. It is worth mentioning that data contradicting the flocculus hypothesis (Miles and Lisberger, 1981) were partly obtained in the ventral paraflocculus (Stone and Lisberger, 1990), whose ablation associated with that of the flocculus caused linked deficits of smooth pursuit eye movements and adaptation of the VOR (Rambold *et al.*, 2002). However, when recorded only from those sites where local electrical stimulation evoked lateral eye movements (suggesting their close connection to the horizontal VOR), the behavior of P-cells was consistent with the flocculus hypothesis (cf. Ito *et al.*, 1993, for ref.). In contrast to this hypothesis, Miles and Lisberger (1981) and Lisberger (1988) postulated that the flocculus target neurons (FTN) localized in the vestibular nuclei represent the critical site for plastic modifications. In favour of this hypothesis was the fact that VOR adaptation could be induced even when retinal slip was prevented by using stereoscopic illumination (Melvill Jones and Mandl, 1979), or by canceling the VOR by mental effort in darkness (Melvill Jones *et al.*, 1984).

Partsalis *et al.* (1995) have shown that in the primate there are at least two modifiable sites in *vertical* VOR pathway, one in the floccular cortex, and the other in the small-celled group Y of the vestibular complex, a structure originally identified by Brodal and Pompeiano (1957) in the cat. According to Partsalis *et al.* (1995), the most likely candidate for the first site is the parallel fiber (PF) synapse onto P-cells (as postulated by Ito), and for the second site a synapse of a head velocity input onto Y group cells, which receives floccular inhibition. The mechanisms underlying changes in these sites rely on retinal slip and visual following, respectively. Accordingly, exposure of an animal to visual-vestibular mismatch results in partial adaptation of the VOR, with visual changes occurring in the cerebellar cortical site, which become complete with changes occurring both in the cortical and the brainstem site.

The hypothesis that brainstem sites intervene in the adaptation of the VOR is supported by the fact that a long-term potentiation (LTP), a neurophysiological substrate for brain plasticity, could be elicited within the vestibular complex (Grassi *et al.*, 2002; Puyal *et al.*, 2003). Of some interest are also the results obtained by Babalian and Vidal (2000) in an *in vitro* whole brain study performed in guinea pig. While these Authors were able to induce a long-term depression (LTD) in P-cells, they failed to detect traces of flocculus-dependent plasticity at the level of FTN neurons in vestibular nuclei by conditioning stimulation of the IO. Although these data do not rule out the possibility of synap-

tic modifications in FTNs and/or in other brainstem sites, they are in favor of the hypothesis that the LTD in the flocculus could be the essential mechanism of cellular plasticity underlying adaptation of the VOR pathway.

The conclusion of these experiments, i.e. that plastic modifications of the VOR occur not only in the flocculus, but also in FTN located in brainstem VN is supported by the results of experiments made by Luebke and Robinson (1994), who used temporary "cerebellar shut-down" as they called it (produced by overstimulation of CF) arising from the IO to ask: (a) would this "shut-down" prevent the induction of adaptive modification of VOR gain? *IT DID*, in accord with everyone else's finding. But, more importantly, their experimental approach was designed to ask: (b) *would a previously induced adaptive modification of gain be abolished by cerebellar shut-down?* *IT WAS NOT*. This led them (a) to confirm that an active cerebellum is *necessary* for the *production* of adaptive gain change, but (b) to conclude that in their experimental design the actual site of plastic change was elsewhere (presumably brainstem) and *NOT* in the cerebellum. However, there are some additional, more recent findings indicating that plastic changes may occur in the cerebellar cortex.

Both McElligott *et al.*, (1998) in goldfish and Nagao and Kitazawa (2003) in monkey, using Lidocaine to produce temporary cerebellar cortex inactivation, showed that: a) this inactivation prevented adaptation (i.e. as every one else), but b) *such inactivation did eliminate the effects of a previously produced adaptation*, thus implicating plastic changes in the cerebellum itself. A significant feature of both these authors' conclusions is that this method of producing adaptation was of short duration. They both suggested that *short-term adaptation* uses cerebellar plasticity, while with *long-term adaptation* this adaptation transfer to brainstem, thus rationalizing the past discrepancies in different research teams, since most past studies in this particular field employed long-term adaptation.

Thus, in spite of the strong controversies between the Japanese and American followings, it seems today (as so often happens in such controversies) that both parties were/are partly correct, the flocculus playing an important role in the *induction* of the adaptation, while the vestibular nuclei to which the flocculus issues its efferents are the side of *retention*. In conclusion, it appears that there are *multiple sites* for modifiable synapses which are located not only in the cerebellar cortex but also in the brainstem vestibular nuclei. Future experiments are required to identify in detail the vestibular nuclear regions which undergo plastic changes contributing to the VOR adaptation.

The most likely candidates in this respect are those structures which project to the cerebellar flocculus. In particular, attention should be devoted in our opin-

ion to the efferent vestibular nucleus (EVe), a site located dorsolateral to the facial genu and ventromedial to the medial vestibular nucleus (MVN) (Goldberg *et al.*, 2000). This nuclear structure sends *efferent* fibers to sensory hair cells, particularly to type II hair cells located in both the cristae and the maculae, which exert centrifugal influences on sensory receptors and their afferents (cf. Wersäll, 1972). Evidence has been presented indicating that the neurons located in the EVe nucleus project not only to the labyrinths, but also send collateral projections to the flocculus (and ventral paraflocculus) bilaterally (Shinder *et al.*, 2001), i.e. to the corticocerebellar structures which are involved in the VOR adaptation. If modifiable changes affect the EVe nucleus neurons in that experimental condition, this would suggest that the sensory stimuli elicited during combined visuo-vestibular stimulation may give rise to plastic changes which affect not only the related corticocerebellar and vestibular structures, but also the sensory hair cells and the corresponding primary vestibular afferents. It would then be of interest to investigate whether the dynamic sensitivity of the vestibular afferents driven during angular and/or linear acceleration could be modified during the conditions involved in the VOR adaptation.

#### SECTION 6. ADAPTATION OF THE VSR DURING COMBINED SOMATOSENSORY AND VESTIBULAR STIMULATION

Changes in head position elicit not only the VOR, which affects the extraocular muscles to stabilize the image of the objects on the retina, but also the VSR, which acts on both the neck and the limb musculature to stabilize the position of the head and the body in space. We have seen that both the VSR and the VOR arcs show a similar pattern of organization as they are made by a three-neuronal chain composed of primary vestibular neurons, secondary vestibular neurons and spinal or extraocular motoneurons. There are, however, differences in the way of operation of the two types of reflexes. According to Ito (1982, 1984), the VSR acting on the neck and the limb extensors during the development of the vestibulo-colic and the vestibular-limb musculature represents a typical closed-loop control system equipped with an efficient feedback from the output to the input, where limb and neck muscle contraction may re-establish the postural adjustments, thus eliminating the input signal. Ito (1984) postulated that under normal conditions this closed-loop control system does not require assistance from the cerebellum. On the other hand, the VOR represents a feed-forward control system, lacking feed-back from output (eye position or velocity) to input (head position or velocity).

We think, however, that the VSR may still require a control from the cerebellum, particularly when somatosensory signals occurring during neck and limb muscle contractions are necessary to produce the appropriate postural changes by interacting with the labyrinthine signals during the development of the VSR. However, while the cerebellar cortex which controls the VOR is located in the flocculus, that which controls the VSR is represented by the zone B of the cerebellar anterior vermis (Corvaja and Pompeiano, 1979; Ito, 1984; Voogd, 1986; cf. Pompeiano, 1969). Moreover, while the P-cells of the flocculus, which receive *direct* primary vestibular afferents, provide inhibitory synapses to the vestibulo-ocular neurons, the P-cells of the cerebellar anterior vermis, which can also be influenced by the labyrinthine signals (Denoth *et al.*, 1979, 1980), via indirect pathways (cf. Pompeiano, 1975b), provide inhibitory synapses to the VS neurons. All the primary and secondary vestibular afferents to the cerebellar cortex terminate as mossy fibers (MF). However, while the flocculus integrates also retinal error signals, which are conveyed in part through climbing fibers (CF), thus being able of modifying the transfer characteristics of MF-parallel fiber signals across the vestibulocerebellum (Graf *et al.*, 1988), the P-cells of the cerebellar anterior vermis receive proprioceptive signals, which can be driven either by the actual displacement of the body over the head (cf. Denoth *et al.*, 1979, 1980), leading to neck signals, or by displacement of the wrist occurring during dorsal flexion and ventral flexion of the forepaw (cf. Bruschini *et al.*, 2000, 2006). We postulated that even in these cases, the corresponding CF signals may modify the transfer characteristics of the MF-parallel fiber signals across the spinocerebellum<sup>1</sup>.

#### a) *Effects of combined neck and vestibular stimulation*

It was previously reported that sustained oscillation of the animal in a platform, surrounded by an optokinetic stimulus field, which rotates out-of-phase or in phase with the platform, represents an efficient condition to elicit adaptive changes of the VOR gain, which increases or decreases respectively, depending on the visual stimulus conditions combined with the sustained head rotation. We decided, therefore, to investigate in a first group of experiments (Andre *et al.*, 1993) whether a sustained rotation about longitudinal axis of the whole animal, leading to sinusoidal stimulation of labyrinth receptors, associated with rotation

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<sup>1</sup>Quite recently Pompeiano *et al.* (1997), Andre *et al.* (1998) and Manzoni *et al.* (1998) have investigated the spatiotemporal response characteristics of the vermal P-cells to animal rotation and neck rotation. They also found that the neck input may modify the reference frame for coding labyrinthine signals in the cerebellar vermis (Manzoni *et al.*, 1999, 2004).

of the body over the head which was out-of-phase or in-phase with respect to the animal displacement, thus leading to sinusoidal stimulation of neck receptors, could produce long-term adaptive changes of the VSR gain. The rationale behind the use of these stimulus combinations lies in the fact that in decerebrate preparations the responses of limb extensors to animal rotation are just opposite in sign with respect to those elicited by neck rotation, for the same direction of animal and neck orientation (Lindsay *et al.*, 1976; Schor and Miller, 1981; Ezure and Wilson, 1983; Manzoni *et al.*, 1983a).

We could then expect that the proprioceptive neck signals, induced by a sustained body-to-head rotation, would have produced a long-term increase or decrease in gain of the VSR according to the direction of that rotation, thus contributing to adjust the gain of the VSR to match the neck displacement.

In decerebrate cats, rotation about the longitudinal axis of the whole animal at 0.15Hz,  $\pm 10^\circ$  produced an increased EMG activity of the triceps brachii (TB) during side-down roll tilt and a decreased activity during side-up tilt. This VSR was tested before, during and after a sustained (3hrs) period of roll tilt of the head at the parameters indicated above, associated with a synchronous roll tilt of the body at 0.15Hz, but at the peak amplitude of either  $12.5^\circ$  (A) or  $7.5^\circ$  (B) (Andre *et al.*, 1993). This additional stimulus led to  $2.5^\circ$  of neck rotation, which was respectively out-of-phase (condition A) or in phase (condition B) with head rotation. In the first instance (A) the gain of the VSR (tested every 10-15 min) progressively increased, starting from the first hour of out-of-phase neck-vestibular stimulation, to reach on average 241% of the control value at the end of the third hour of stimulation. On the other hand in B, the mean gain of the VSR decreased to 82% during the first hour of in-phase neck-vestibular stimulation, but then increased to 165% of the corresponding control during the last hour of recording. The adaptive increase in gain of the VSR described above was not associated with changes in the phase angle of the responses, and remained stationary for least one hour after the end of the adaptation period.

The adaptive changes in gain of the VSR produced in decerebrate cats by a sustained neck-vestibular stimulation should then be compared with those which affect the VOR gain during sustained horizontal rotation of an intact animal with stationary or sinusoidally moving visual field (Ito *et al.*, 1974, 1979; cf. Ito, 1982, 1984). In these instances the VOR gain increased with *synergistic* visual-vestibular interaction (turntable rotation with stationary or out-of-phase moving screen), but decreased with *antagonistic* interaction (in-phase screen rotation with the same or twice the amplitude of that of the turntable).

Attempts were made to identify the site where the plastic changes which are

responsible for the adaptation of the VSR during combined neck-vestibular stimulation occur. We have seen that convergence and interaction of neck and vestibular inputs occur at the level not only of the excitatory VS neurons (Boyle and Pompeiano, 1981a, b; Marchand *et al.*, 1987), but also of presumably inhibitory reticulospinal (RS) (Manzoni *et al.*, 1983b; Pompeiano *et al.*, 1983, 1984; Srivastava *et al.*, 1984) and excitatory coerulespinal (CS) neurons (Barnes *et al.*, 1985; Manzoni *et al.*, 1989; Pompeiano *et al.*, 1990), the role of which in the gain regulation of the VSR has been reported in detail in recent review articles (Pompeiano 1990, 1992a, 1992b; cf. also Pompeiano, Horn, d'Ascanio, 1991). Adaptive changes of the VSR gain may occur either at the level of the excitatory VS neurons, which play an executive role in the development of that reflex, or at the level of the inhibitory RS and/or the excitatory CS neurons, which apparently play a permissive role in the gain control by acting through Renshaw cells (cf. Pompeiano 1984, 2000). An additional or alternative possibility, however, is that the plastic changes occur at the corticocerebellar level.

We have seen that the P-cells of the zone B of the cerebellar anterior vermis respond to roll tilt of the animal with a predominant response pattern which was opposite in sign to that of the VS neurons (Denoth *et al.*, 1979, 1980). The same neurons may also respond to neck rotation, by utilizing both the MF as well as the CF (Denoth *et al.*, 1979, 1980; Bruschini *et al.*, 2006). The proprioceptive neck input evoked during sustained out-of-phase neck-vestibular stimulation could not only increase the proportion of P-cells showing an out-of-phase modulatory response to labyrinthine stimulation, but also give rise to an efficient process of adaptation, whatever the actual site of the adaptable synapses might be. Thus the zone B of the cerebellar anterior vermis may represent a modifiable side-path of the VSR system, capable of adjusting the corresponding gain to match the neck displacement. This neuronal model is reminiscent of that proposed for the VOR, in which case the corticocerebellar area which integrates the labyrinthine signals is represented by the flocculus (Ito, 1982, 1984) <sup>2</sup>.

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<sup>2</sup>The adaptive changes in gain of the VSR produced in a decerebrate cat by a sustained neck-vestibular stimulation can be relevant in order to understand the mechanisms by which the postural and motor deficits induced after unilateral labyrinthectomy (UL) are compensated. In particular, when soon after the labyrinthine lesion, the animal head is rotated towards the lesioned side (Schaefer and Meyer, 1981) and the pattern of the VSR acting on the contralateral limbs is severely disrupted (Berthoz and Anderson, 1972; Lindsay and Rosenberg, 1977), rhythmic head movements may occur. In these instances the resulting neck signals would lead to plastic changes, which may affect the gain of the VSR acting on limb extensors. In these instances a bilateral neck deafferentation performed in a compensated animal produces the reappearance of the postural deficits following UL (Schaefer and Meyer, 1981).

b) *Effects of combined forepaw and vestibular stimulation*

The VSR arc is under the adaptive control of somatosensory signals originating not only from neck receptors (Andre *et al.*, 1993), but also from the limb extremities (Manzoni *et al.*, 2005). Observations made in decerebrate cats have shown that the TB activity increases not only during side-down roll tilt of the whole animal (at 0.15 Hz,  $\pm 10^\circ$ ), while decreasing during side-up tilt (cf. Manzoni *et al.*, 1983). The same TB activity also increases during dorsal flexion of the ipsilateral forepaw (0.15 Hz,  $\pm 5-10^\circ$ ), but decreases during ventral (plantar) flexion (d'Ascanio *et al.*, 1985; Bruschini *et al.*, 2001, 2006). Moreover, the responses of the TB to forepaw rotation add almost linearly to those induced by roll tilt of the animal (Bruschini *et al.*, 2001). Synergistic stimulation of labyrinthine and forepaw (wrist) receptors during a 3h period of this sustained stimulation (side-down tilt of the whole animal coinciding with dorsal flexion of the forepaw) progressively increased the amplitude of the pure VSR, which reached on the average the maximum value of + 272% of the control at the end of the third hour of stimulation. This value remained almost unmodified during the post-adaptation period (90 min) (Manzoni *et al.*, 2005). On the other hand, when animal tilt and forepaw (wrist) rotation were *antagonistically* associated (side-down tilt coinciding with ventral flexion of the forepaw), the VSR gain remained on the average stable, but at the end of the 3 hrs period of combined stimulation a proportion of TB responses to animal tilt showed a phase reversal.

We postulate that in a digitigrade animal like the cat, a dorsal flexion of the wrist associated with a decrease in limb length would occur when during the VSR the extensor tone is not appropriate to support the body weight. In this case the somatosensory signals arising from wrist rotation would act as an "error signal", which promotes the development of compensatory adjustments of the VSR gain, so as to maintain postural stability.

In analogy with the results obtained during synergistic stimulation of neck and vestibular receptors (Andre *et al.*, 1993), synergistic stimulation of forepaw and vestibular receptors can also give rise to an adaptive increase in gain of the VSR (Manzoni *et al.*, 2005). It is of interest that functional inactivation of the zone B of the cerebellar anterior vermis (lobules IV and V), following local microinjection of GABA-agonists, decreased or suppressed not only the basal (Andre *et al.*, 1994; Manzoni *et al.*, 1997), but also the already adapted VSR gain elicited during synergistic neck-vestibular (Manzoni *et al.*, 1994) and wrist-vestibular stimulation (Manzoni *et al.*, 2005). This finding can be understood if we consider that the P-cells located in this region receive not only convergent neck

and vestibular signals (Denoth *et al.*, 1979; Manzoni *et al.*, 1998), which control the activity of VS and RS neurons (Pompeiano, 1969; Corvaja and Pompeiano, 1979; Voogd, 1986; cf. Ito, 1982), but also somatosensory signals which utilize both the MF and the CF, during forepaw displacement (Bruschini *et al.*, 2000, 2006). It is not surprising, therefore, to observe that the cerebellar vermis is important for the development and the maintenance of the plastic modifications in VSR gain induced by combined neck-vestibular and forepaw-vestibular stimulations.

In conclusion, the results of our experiments indicate that an adaptive increase in gain of the VSR occurred not only when the proprioceptive neck signals failed to keep the forelimb sufficiently extended to stabilize the position of the trunk over the limbs, but also when the extensor tonus of the forelimbs was not appropriate to support the body weight during dorsal flexion of the forepaws. In both instances the somatosensory signals arising from either neck rotation or wrist rotation may act as "error signals", which promote the development of compensatory adjustments of the VSR gain, so as to maintain postural stability. From this point of view the proprioceptive signals which contribute to the adaptation of the VSR operate as the visual signals which occur when the retinal slip indicates a failure of gaze stabilization, thus leading to adaptation of the VOR gain (Ito *et al.*, 1974, 1979; Collewyn and Grodendorst, 1978).

Summing up, the somatosensory inputs to the cerebellar vermis, originating either from the neck or wrist rotation can be used to plastically modify the gain of the VSR. In particular, both neck and forepaw signals may lead to an adaptive increase in gain of the VSR, when these proprioceptive signals are not efficient enough to produce appropriate adjustments of the VSR gain during combined neck-vestibular or forepaw-vestibular stimulation (Andre *et al.*, 1993; Andre *et al.*, 2005). These adaptive changes closely resemble those which affect the VOR during sustained visuo-vestibular stimulation (Ito, 1982, 1984). Thus the zone B of the cerebellar anterior vermis can be viewed as an inhibitory side-loop of the VSR pathway, in the same way as the flocculus has been viewed by Ito as an inhibitory side-loop of the VOR pathway.

#### SECTION 7. LONG-TERM DEPRESSION (LTD) CONTRIBUTING TO ADAPTATION OF THE VESTIBULO-OCULAR REFLEX (VOR)

The long-term synaptic plasticity is a biological process, characterized by persistent changes in synaptic strength which follow specific forms of neuronal and synaptic activation. This process, which is considered at the basis of learning

and memory, is represented by two forms of either long term potentiation (LTP) or depression (LTD), which have been reported in several central synapses located either in the cerebellum (present review) or in other brain structures, such as the neocortex and the hippocampus (see Section 12).

According to Hebb's (1949) rule, both the pre- and postsynaptic neurons have to discharge together, intensely and repeatedly, to produce LTP. LTD, however, arises in the opposite case of weak, asynchronous, sporadic activity in the two elements. We have seen that both the corticocerebellar areas corresponding to the flocculus, as well as to the zone B of the cerebellar anterior vermis, undergo adaptive changes which affect the VOR (Section 4) and the VSR (Section 6) during combined visuo-vestibular and somatosensory-vestibular stimulation, respectively.

Ito's (1982, 1984; Ito *et al.*, 1982, 1989) model of the cerebellum as a putative basis for general adaptive motor control was founded on the earlier basis of Marr's theoretical proposal (1969), i.e. that simultaneous related signals arriving at the cerebellar cortex through parallel fibers (PF) and CF, produced changes of PF-P cell synapses. Actually it was a little known speculative suggestion by Brindley (1964) at Cambridge University, that stimulated Marr to put forward this hypothesis. According to Marr's original proposal, a characteristic synaptic plasticity in the form of LTD was found to affect the neuronal transmission from PF to P-cells, when the PF synapses were activated conjunctively with activation of the synapses of the CF (axons of the IO neurons in medulla) (Ito *et al.*, 1982; Ito, 1989; Nagao and Ito, 1991). In particular, while the vestibular input activates P-cells through MF, the flocculus (or the cerebellar anterior vermis) receive error signals which originate from visual receptors (or somatosensory neck and wrist receptors) and may utilize CF to subserve the recalibration of the VOR (or the VSR), respectively. The metabolic chains involved in regulating synaptic transmission to P-cells showed unexpected complexities.

Observations by Ito (1989, 2001, 2002) have shown that LTD was due to a sustained *desensitization* of glutamate receptors at the parallel fiber (PF) synapse on P-cell dendrites. This finding occurred during the CF impulses, which cause  $\text{Ca}^{2+}$  to enter P-cell dendrites through voltage-dependent  $\text{Ca}^{2+}$  channels (Stöckle and ten Bruggencate, 1980).  $\text{Ca}^{2+}$  entry in the P-cell dendrites caused by membrane depolarization would trigger intracellular *enzyme reactions*, which could play roles in facilitating desensitization of glutamate receptors (Crépel and Krupa, 1988; Linden and Connor, 1991). It is known that cerebellar P-cells are rich in cyclic GMP-dependent protein kinase type I (cGKI or PKG) (Hofmann

and Sold, 1972; Lohmann *et al.*, 1981; Feil *et al.*, 2003), and its specific G-substrate (Lohmann *et al.*, 1981; Nairn *et al.*, 1985). It appears also that protein kinases and phosphatases acting together regulate the level of phosphorylation of proteins including synaptic receptors (Cohen, 1989; Huganir and Greengard, 1990; cf. also Hausdorff *et al.*, 1990). When phosphorylated by PKG, G-substrate acts to inhibit protein phosphatases. In addition to PKG, P-cells also contain cyclic AMP-dependent protein kinase (PKA) (Caretta *et al.*, 1991) and protein kinase C (PKC) (Crépel and Krupa, 1988; Lender and Connor, 1991; Hartell, 1994b; Kose *et al.*, 1988)<sup>3</sup>.

Detailed observations by Ito and Karachot (1989) have shown that application of quisqualate (QA) to cerebellar slices induces long-term desensitization of glutamate receptors mediating the PF-P cell response, an effect which lasted for at least 10 h without recovery (Ito and Karachot, 1990a). According to these Authors, QA stimulates two subtypes of glutamate receptors, one being *ionotropic* and selective to AMPA ( $\alpha$ -amino-3hydroxy-5-methyl-4-isoxazolepropionic acid (Ito and Karachot, 1990), while the other is *metabotropic* and prefers t-ACPD (trans-1-amino-cyclopentyl-1,3-decarboxylic acid (Sugiyama *et al.*, 1987; Vranesic *et al.*, 1991).

Evidence has been presented indicating that QA-induced long-term desensitization occurs specifically in AMPA receptors through a process which involves t-ACPD receptors (Ito and Karachot, 1990b). In particular, activation of these receptors could trigger an intracellular chain reaction, which comprises production of inositol – 1, 4, 5 – triphosphate ( $IP_3$ ),  $Ca^{2+}$  release from intracellular stores, generation of nitric oxide, NO (the gaseous diffusible neurotransmitter produced by nitric oxide synthase, NOS), synthesis of cyclic GMP and finally activation of cyclic GMP-dependent protein kinase (PKG) (cf. Ito and Karachot, 1990b for ref.). PKG would in turn act upon AMPA receptors through phosphorylation (cf. Ito and Karachot, 1990a, b, 1992; Nakazawa *et al.*, 1995).

In line with these conclusions are the results of findings showing that the two messengers  $Ca^{2+}$  and NO are relevant to induce LTD (Lev-Ram *et al.*, 1995). Furthermore, genetic ablation of neuronal NOS impaired LTD (Lev-Ram *et al.*, 1997b) and adaptation of compensatory eye movements (Katoh *et al.*, 2000). Experiments with cerebellar slices have also shown that NO-cGMP-protein kinase G cascade is required for LTD induction (Shibuki and Okada, 1991; Hartell, 1996; Lev-Ram *et al.*, 1997a; Hartell *et al.*, 2001). Moreover, NO

<sup>3</sup> However, observations by De Zeeuw *et al.* (1998) have shown that LTD was absent in a transgenic mouse that selectively expressed an inhibitor of protein kinase C (PKC) in P-cells.

induced LTD via activation of soluble guanylylcyclase and subsequent synthesis in P-cells (Daniel *et al.*, 1993; Boxal and Garthwaite, 1996). It appeared also that knock-out mice, lacking cGKI, i.e. cyclic GMP-dependent protein kinase type I in P-cells, exhibited a reduced cerebellar LTD and an impaired adaptation of the VOR (Feil *et al.*, 2003). Moreover, agents that inhibit cGKI impaired LTD, i.e. the activity-dependent attenuation of synaptic transmission at the PF-Pcell synapse (Hartell, 1994b; Lev Ram *et al.*, 1997a). Further data reported by Feil *et al.* (2003) indicate that group I metabotropic glutamate receptors (mGlu R1) in cerebellar P-cells are essential for LTD (cf. also Alba *et al.*, 1994; Conquet *et al.*, 1994; Hartell, 1994a; Ichise *et al.*, 2000), as shown by the fact that this depression was prevented by an antagonist of mGlu R1 (cf. Gao, 2003), and was absent in transgenic mice that selectively expressed an inhibitor of protein kinase C (PKC) in P-cells (cf. Masu *et al.*, 1991; De Zeeuw *et al.*, 1998).

It is worth to mention that the Marr's model (1969) did not include any MF-granule cell synaptic plasticity, although the subsequent extension by Albus (1971) was more permissive. In particular, it appears that the postsynaptic targets of PF include not only P-cells, but also inhibitory interneurons, which in turn exert a strong inhibitory influence on P-cells and PF (Eccles *et al.*, 1966). Gao *et al.*, (2003) used neutral red optical imaging of the cerebellar cortex in anesthetized rats to visualize the spatial pattern of activation which occurs in the cerebellar cortex following conjunctive stimulation of CF and PF. They found that the long-term decrease in the optical response to parallel fiber activation which occurred after this conjunctive stimulation was primarily attributable to LTD of PF-P-cell synapses (Ito and Kano, 1982; Ekerot and Kano, 1985; Karachot *et al.*, 1994), rather than to rebound potentiation of GABA-A receptor mediated interneuron-P-cell synapses (Kano *et al.*, 1992), i.e. to a form of LTD of PF-inhibitory interneuron synapses. However, the observation that the MF discharge consists of high frequency bursts and that granule cells express NMDA receptors which trigger the induction of LTP/LTD at other central synapses, led some authors to revisit the question. In fact, high frequency stimulation applied to MF in cerebellar slices persistently strengthened granule cell synaptic excitation, indicating the occurrence of LTP at the MF-granule cell synapse of cerebellum (Hansel *et al.*, 2001; Gall *et al.*, 2005; cf. D'Angelo, 2005 for ref.). This may open new perspectives on the relationship between synaptic structure, function and plasticity in the cerebellar cortex.

An interesting comment advanced by Ito and Karachot (1990) is that glutamate receptors may not necessarily be stimulated by neurotransmitter release from PF, if they are located remote from PF-P cell synapses. To overcome this diffi-

culty, it has been postulated, that CF release a still unknown neurotransmitter, which would activate metabotropic glutamate receptors (cf. Ito 1984, pag 127, Fig 58B). Evidence reported in our Section 9 indicates that this action could be exerted by norepinephrine (NE). Additional experiments have shown that members of the G-protein coupled group I metabotropic glutamate receptors exert a role in the LTD of the parallel fiber-to P-cell transmission (Hartmann *et al.*, 2004), and that these proteins may utilize NE (and GABA) for reducing the P-cell output during VOR adaptation (cf. Zhou *et al.*, 2003, for ref.).

#### SECTION 8. EXPRESSION OF IMMEDIATE EARLY GENES (IEGs) IN CEREBELLAR P-CELLS DURING LTD

After the demonstration that LTD was due to desensitization of glutamate receptors on cerebellar P-cells, Nakazawa *et al.* (1993) used *in situ* hybridization and immunohistochemical techniques to study the expression *in vitro* of immediate early genes (IEGs) following the synaptic LTD evoked by co-administration of AMPA and 8-bromo cGMP. These agents, mimicking heterosynaptic activation of P-cells (Ito and Karachot, 1990, 1992), synergistically enhanced the expression of c-Fos and Jun B in P-cells within 30 min after application of the two agents. These experiments were repeated in more physiological conditions, i.e. *in vivo*, by Yamamori *et al.* (1995), who substituted CF activation for the application of 8 Br-cGMP used previously by Nakazawa *et al.* (1993). They report an increased local induction of c-fos and Jun-B in P-cells, when electrical stimulation of the IO was conjunctively applied with AMPA in the cerebellar cortex. It appeared also that the Jun B expression, which resulted from costimulation of CF and axons of granule cells, was blocked by a NOS inhibitor (Yano *et al.*, 1996). It is known that Jun-B forms with c-Fos an heterodimer transcriptional factor, called AP-1-complex (Morgan and Curran, 1989, 1991), the protein products of which may function as third messengers, to regulate the transcription of target genes. Since the latter genes control cellular function, the c-fos and Jun-B induction may represent a molecular mechanism by which short-term signals at the cell membrane are transduced into long-term biochemical changes to transynaptic signals (Ito and Karachot, 1990a, b), that are required for cerebellar long-term plasticity (cf. Pompeiano, 1994, 1998, 2000; Ito 2001, 2002).

The cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) is a nuclear protein regulating the transcription of genes with a CRE site in their promoter. When synaptic activation causes a high  $[Ca^{2+}]_i$ ,

CREB is phosphorylated at its transcriptional regulatory residue (serine-133) by involving the  $\text{Ca}^{2+}$ -calmodulin-dependent protein kinase type IV (CaMKIV). There is now evidence that CREB and CaMKIV contribute to the late phase of LTD (Ahn *et al.*, 1999; Ho *et al.*, 2000; cf. Sakagami and Kondo, 1993; Ribar *et al.*, 2000), a mechanism that weakens the neurotransmission of excitatory synapses made by parallel fibers on target neurons.

SECTION 9. ROLE OF THE NORADRENERGIC LOCUS  
COERULEUS (LC) SYSTEM IN PLASTICITY CHANGES WHICH  
AFFECT THE CEREBELLAR CORTEX DURING ADAPTATION  
OF THE VESTIBULAR REFLEXES

Two possibilities have been proposed by Ito (1982, 1984) to account for the LTD which occurs in subsynaptic sensitivity of P-cells during vestibular adaptation. The *first* possibility postulates that CF activation of P-cells produces a voltage-dependent increase of the calcium permeability of the dendritic membrane (ten Bruggencate *et al.*, 1976; Stöckle and ten Bruggencate, 1980). The increased intradendritic calcium concentration which occurs during the long-lasting plateau potential that characterizes the complex spike following CF activation affects subsynaptic receptors of P-cell dendrites in the manner suggested for desensitization phenomena in neuromuscular junctions (Miledi, 1980; Ekerot and Oscarsson, 1981) (see Fig. 58A in Ito, 1984). The *second* possibility is that CF release a chemical substance (see Fig. 58B in Ito 1984) which reacts with both subsynaptic receptor molecules and parallel fiber neurotransmitter (Ito, Sakurai and Tongroach, 1982). Ekerot and Kano (1983) have shown that when the CF-induced plateau potential in P-cell dendrites was abolished by conditioning stellate inhibition, the LTD could no longer be induced by conjunctive stimulation of CF and PF. This finding, however, does not exclude the *second* possibility.

It is known that CF activation causes not only a significant decrease of extracellular  $\text{Ca}^{2+}$  concentration in the cerebellar cortex, but also a prominent increase of extracellular  $\text{K}^{+}$  concentration, due to movement of  $\text{K}^{+}$  ions out of P-cell dendrites, during the depolarization-dependent and  $\text{Ca}^{2+}$ -dependent increase of the membrane  $\text{K}^{+}$  conductance (Stöckle and ten Bruggencate, 1980). Quite recently a new category of  $\text{K}^{+}$  channels, represented by Two Pore Domain Potassium Channels (2PDKCs) have opened new perspectives in the research of molecular correlates responsible for changes in putative  $\text{K}^{+}$  currents (Ketchum *et al.*, 1995; Talley *et al.*, 2000; Meuth *et al.*, 2003; Kang *et al.*,

2004). After the demonstration that 2 PDKCs also operate at corticocerebellar level (Millar *et al.*, 2001), it would be of interest to investigate whether changes in the expression of the corresponding genes may occur during adaptation of the VOR with respect to the non-adapted reflex condition.

Experimental anatomical studies have shown that the noradrenergic LC neurons project to the whole cerebellar cortex (cf. Foote *et al.*, 1983; Barnes and Pompeiano, 1991), and that P-cells located in both the flocculus and the cerebellar vermis are surrounded by a dense network of unmyelinated nerve terminals. There is also evidence that  $\beta$ -adrenergic receptors ( $\beta$ AR) are concentrated around the P-cell somata (Atlas, Theichberg and Changeaux, 1977). We postulated that the increase in extracellular  $K^+$  which occurs during CF activation of P-cells (i.e. during adaptation of the vestibular reflexes) induces a local depolarization of the noradrenergic *unmyelinated* nerve terminals leading to release of norepinephrine (NE) (d'Ascanio, Arrighi and Pompeiano, 1998a). This agent, which acts on  $K^+$  conductance (Talley *et al.*, 2000) may not only increase the responsiveness of the P-cells to glutamatergic afferent signals, but also contribute to the plastic events responsible for vestibular adaptation (cf. Pompeiano, 1994, 1998, 2000).

The hypothesis that the noradrenergic system exerts a prominent role in the regulation and adaptation of the VOR and the VSR occurring during combined visuo-vestibular and somatosensory-vestibular stimulation and that these effects are mediated by  $\beta$ -adrenoceptors have originally been tested in our previous studies. Observations made by Van Neerven, Pompeiano, Collewyn and Van der Steen (1990) have, in fact, shown that bilateral intrafloccular microinjection of a  $\beta$ -adrenergic agonist (isoproterenol) or antagonist (sotalol) in adult belted rabbits increased or decreased, respectively, the amplitude of the VOR adaptation, particularly if evaluated in darkness. The same injections, however, did not modify the steady state gain values, indicating that the  $\beta$ -noradrenergic system exerted a specific influence on the VOR adaptation elicited during visual-vestibular stimulation. *These findings were never included by Ito in his flocculus hypothesis.* In contrast to the noradrenergic agents indicated above, which bind aselectively to both  $\beta_1$  and  $\beta_2$  receptors, the  $\alpha_1$  and  $\alpha_2$  receptors were apparently not involved in the VOR adaptation, as shown by intrafloccular injection of appropriate agonists or antagonists (Tan, Van Neerven, Collewyn and Pompeiano, 1991). In analogy with these findings, unilateral intravermal microinjection of the  $\beta$ -adrenergic antagonists, propranolol or sotalol, prevented in decerebrate cats the occurrence of the adaptive increase in gain in the VSR, elicited during roll tilt of the animal, associated with a body-to-head rota-

tion, leading to out-of-phase stimulation of neck receptors (Pompeiano *et al.*, 1994a, b).

The demonstration that microinjection into the flocculus and the cerebellar vermis of  $\beta$ -adrenergic antagonists prevents the occurrence of adaptive changes in gain of the VOR and the VSR, respectively, raises the question as to whether NE contributes to the chain of events, which involve excitatory aminoacid receptors and certain second messenger systems at the P-cells thus underlying the LTD, which occurs during vestibular adaptation. In fact, there is evidence that the noradrenergic LC neurons act on corticocerebellar neurons through  $\beta$ -activation of a cAMP-dependent mechanism (Summers and Martin, 1993), to increase c-fos and Jun B-expression which may occur during vestibular adaptation (see Pompeiano, 1994, 1998, 2000, and Section 7). This hypothesis is supported by the fact that activation of the noradrenergic system in some brain structures, such as the cerebral cortex of the rat, locally increased the expression of both the c-fos mRNA and the Fos protein level, an effect that was predominantly mediated through  $\beta$ -adrenoceptors (Hughes and Dragunow, 1995) (see also Section 11).

A detailed study of the cellular responses to the catecholamines was made by Hausdorff *et al.* (1990), who found that brief exposure to NE and epinephrine of plasma membrane proteins which included the  $\beta$ AR membrane, the stimulatory guanine-nucleotide binding protein  $G_s$ , and the enzyme adenylylcyclase (AC), which catalyzes the formation of cAMP from ATP, results in profound increases in the intracellular concentration of the classical second messenger cAMP, which *wane* rapidly within a few min despite continuous exposure of P-cells to these stimuli. The molecular mechanisms underlying this rapid  $\beta$ AR *desensitization* do not appear to require internalization of the AMPA receptors, as shown in cultured P-cells (Matsuda *et al.*, 2000; Wang and Linden, 2000), but rather an alteration of the functioning of  $\beta$ AR themselves, that uncouples the receptors from the stimulatory G protein,  $G_s$ . This uncoupling phenomenon involves the phosphorylation of  $\beta$ AR by at least two-kinases, PKA and  $\beta$ AR kinase ( $\beta$ -ARK), which are activated under different desensitizing conditions. The molecular mechanisms operating at the receptor level have been implicated in *short-term* and *long-term* desensitization (Klein *et al.*, 1989). In particular, it appears that the desensitization of the AC response, i.e. the very rapid attenuation of the AC response elicited by a short-term exposure to agonists, disappears in min after removal of the desensitizing agonist and without a requirement for new protein synthesis. However, recovery from the profound desensitization induced by prolonged exposure to agonist requires new protein synthesis and may take hours or days (Perkins *et al.*, 1993).

As reported in Section 7, a desensitization of glutamate receptors leading to LTD utilizes not only ionotropic (AMPA) but also metabotropic mGlu R1 receptors. NE may through  $\beta$ AR contribute to the desensitization of the P-cells to glutamate receptors, as reported during the VOR adaptation. Moreover, by increasing the expression of IEGs (Section 8), NE may encode transcription factors that are likely to control the expression of late response genes, the protein products of which are likely to mediate long-term neuronal responses.

It would be of interest to investigate whether the adaptability of the vestibular reflexes in mammals is reduced or suppressed: 1) by a selective lesion of the LC which could markedly attenuate the induction of Fos-like immunoreactivity in the cerebellar cortex, as shown in the neocortex of rat under conditions that produce a local release of NE (Stone *et al.*, 1993; cf. also Cirelli *et al.*, 1996, 2000); 2) by interfering with the molecular mechanisms by which second messenger pathways activated by  $\beta$ AR regulate the expression of IEGs such as c-fos and Jun-B (Hughes and Dragunow, 1995), and 3) by blocking the expression of Fos protein in the cerebellar vermis and flocculus, with local injections of c-fos antisense oligonucleotides complementary to c-fos mRNA (Cirelli, Pompeiano, Arrighi *et al.*, 1995).

#### SECTION 10. RESPONSES OF NORADRENERGIC LC NEURONS TO LABYRINTH AND OTHER SENSORY STIMULATIONS

The hypothesis that the noradrenergic LC system is involved in the adaptation of the vestibular reflexes is supported by the results of electrophysiological experiments performed in decerebrate cats, showing that the noradrenergic LC neurons respond with changes in firing rate to natural stimulation of labyrinth receptors. In particular, we discovered that LC neurons responded to both static and dynamic stimulations of labyrinth receptors (Pompeiano and Hoshino, 1976; Manzoni *et al.*, 1989; Pompeiano *et al.*, 1990). These effects could be mediated either by activation of a direct projection of vestibular nuclei (VN) to the LC (Fung *et al.*, 1987) or by indirect projections passing through medullary reticular structures (cf. Pompeiano *et al.*, 1990; d'Ascanio *et al.*, 2002). LC neurons may also respond to visual signals (Aston-Jones *et al.*, 1991; Barnes and Pompeiano, 1991) as well as to proprioceptive neck signals (Manzoni *et al.*, 1989; Barnes *et al.*, 1989), thus being able of contributing to the afferent volleys responsible for adaptation of the VOR and the VSR, respectively.

It is likely, therefore, that both the flocculus and the cerebellar anterior vermis receive noradrenergic signals not only through the local mechanisms postulat-

ed in Section 9, but also through a reflex activation of LC neurons, which is likely to occur during sustained out-of-phase visuo-vestibular or proprioceptive neck-vestibular stimulation (Sections 4 and 6). The role that the noradrenergic LC neurons exert in the induction of IEGs acting on their target structures will be discussed in Section 11.

#### SECTION 11. NORADRENERGIC SIGNALS FROM THE LC INDUCE THE EXPRESSION OF IMMEDIATE EARLY GENES (IEGs) IN THEIR TARGET STRUCTURES

It is known that changes in neuronal activity in the CNS are associated with changes in the rates of transcription of both IEGs and their protein products. Several IEGs, such as c-fos, c-Jun, NGF Ia and -Ib, Arc, Zif-268 and others are activated by neuromodulators (cf. for ref. Cirelli and Tononi, 2000; Berridge and Waterhouse, 2003). These IEGs regulate transcription rates of a variety of genes, so that relatively short-term alteration in neuronal discharges are transduced into long-term biochemical events that underlie plasticity (Dragunow *et al.*, 1989; Morgan and Curran, 1989, 1991; Guzowski *et al.*, 2001).

One of the neuromodulators which exert a prominent role in the regulation of short-term or long-term plasticity, as well as in the behavioral processes depending on plasticity is represented by norepinephrine (NE). For example, increased release of NE elicited by systemic administration of an  $\alpha_2$  antagonist increased c-fos, nur 77, tis-7, tis-21 and Zif-268 mRNA (Bing *et al.*, 1991; Gubits *et al.*, 1989) and protein levels (Bing *et al.*, 1992) in the rat cerebral cortex. Direct infusion of NE in the cerebral cortex (Rainbow *et al.*, 1983) and amygdala (Stone *et al.*, 1997) also elicited a similar increase in c-fos mRNA. The activating effects of NE on IEG expression was attenuated by pretreatment of either  $\beta$  or  $\alpha_1$  antagonists or by LC lesion (Stone *et al.*, 1993).

Additional studies implicate the  $\beta_1$ -receptor subtype in  $\beta$ -dependent activation of c-fos (Stone *et al.*, 1995).

We have seen that the adaptation which affects the VOR during combined visuo-vestibular stimulation is due to plastic changes which affect the cerebellar flocculus and that this effect is partly mediated by the noradrenergic LC system, which exerts a prominent role in the induction of IEGs. Is it possible to prove that in the intact unanesthetized animal the sensory signals which contribute to the VOR adaptation also increase the level of wakefulness and that this state may not only determine an increased discharge of the noradrenergic

LC neurons, but also potentiate the induction of IEGs in the corresponding target structures particularly located in the cerebellar cortex?

Electrophysiological experiments have shown that in adult rats the LC neurons fire regularly at very low rate during sleep, but reach the higher level during waking (cf. Hobson *et al.*, 1975; Aston-Jones and Bloom, 1981; Foote *et al.*, 1980, 1983; Hobson and Steriade, 1986; Berridge and Waterhouse, 2003). It appears also that LC activation following infusion of the cholinergic agonist bethanechol into the LC region produces EEG changes characterized by high-frequency, low-amplitude EEG activity in the frontal neocortex and by the appearance of intense ( $\rho$ , theta) rhythm in the hippocampus (Berridge and Foote, 1991). These effects were blocked by pretreatment either with the  $\alpha_2$ -agonist clonidine, which inhibits the LC discharge and NE release, or with the  $\beta$ -antagonist propranolol. These findings indicate that LC activation may be sufficient to induce EEG signs of cortical and hippocampal activation. The sensory stimuli which contribute to the VOR adaptation are likely to potentiate the waking state.

Experiments of molecular biology have shown that in most brain regions which receive a diffuse noradrenergic innervation (such as in the cerebral cortex and the hippocampus, as well as in the LC), the expression of some transcription factors such as the c-fos and nerve growth factor-induced A (NGFI-A), which mediate long-term changes in neural function, was much greater during the waking state than during sleep (cf. Pompeiano M., Cirelli and Tononi, 1994). An increased discharge of noradrenergic LC neurons (Abercrombie and Jacobs, 1987; Chen and Herbert, 1995; Stone and Zhang, 1995), as well as an increase in IEG expression (Bing *et al.*, 1991, 1992; Gerbits *et al.*, 1980) were also observed during exposure of the animals to stress.

An important pathway by which NE release during waking may facilitate the induction of IEGs in ground-based experiments involves the phosphorylation of the cyclic adenosine monophosphate (cAMP) response element-binding protein (P-CREB), which can act on the promoters for c-Fos and NGFI-A. Unilateral injection into the LC of rats of 6-hydroxydopamine (6-OHDA), a neurotoxin that destroys catecholaminergic neurons, decreases the concentration not only of Fos and NGFI-A, but also of P-CREB in cortical areas depleted of noradrenergic fibers (Cirelli, Pompeiano M. and Tononi, 1996, 2000). Similar result occurred also after unilateral injection into the LC of rat of DSP-4 (Cirelli and Tononi, 2004), another neurotoxin that destroys selectively the noradrenergic LC neurons (cfr. Barnes and Pompeiano, 1991 for ref.). Given the similar distributions of Fos expression during waking and of  $\beta$ -noradrenergic receptors

into the cerebral cortex (cf. Palacios *et al.*, 1980; Rainbow *et al.*, 1984; Aoki *et al.*, 1987), it has been suggested that NE released by LC terminals during waking may induce Fos by acting through a pathway that leads from  $\beta$ -adrenergic receptors to CREB phosphorylation. The modality by which the noradrenergic system may through  $\beta$ -adrenoceptors induce the gene expression in the forebrain structures such as the neocortex and the hippocampus during the waking state (as reported in this section) is quite similar to that reported within the cerebellar cortex of the flocculus during the VOR adaptation (Section 8).

It is worth mentioning that 6-OHDA-induced depletion of brain NE, which suppressed the gene expression during waking, did not apparently alter the EEG pattern of desynchronization associated with waking (Cirelli, Pompeiano M. and Tononi, 1996). However, pharmacological and lesion experiments, have shown that 6-OHDA induced depletion of brain NE or electrical destruction of the LC decreased the incidence of low-amplitude, high-frequency EEG activity in some studies but not in others (Berridge and Foote, 1991). These contradictory results could be related to compensatory mechanisms that act to minimize the functional consequence of NE-specific lesions (Vanderwolf and Robinson, 1981).

#### SECTION 12. EVIDENCE THAT THE GENES EXPRESSED BY NOREPINEPHRINE (NE) IN FOREBRAIN STRUCTURES ARE INVOLVED IN VARIOUS FORMS OF NEURAL PLASTICITY

As reported in the previous section, the noradrenergic LC neurons project not only to the cerebellum but also to forebrain structures, such as the cerebral cortex (neocortex) and the hippocampus (cf. Foote *et al.*, 1983; Barnes and Pompeiano, 1991). NE (as well as Ach) act as neuromodulatory transmitters which can modulate the excitability of cortical neurons, enhance the signal-to-noise ratio of cortical responses, and modify the threshold for activity-dependent synaptic modifications (cf. Steriade *et al.*, 1993). These effects are mediated via numerous subtype receptors which are linked to multiple signal transduction mechanisms. NE released within the cerebral cortex and the hippocampus intervenes not only in the modulation of behavioral states, such as those occurring during the sleep-waking activity (see Section 10), but also during state-dependent cognitive processes, including learning and memory (cf. Berridge and Waterhouse, 2003; Cirelli and Tononi, 2004).

Specific forms of activity-dependent synaptic plasticity have been reported in the cerebral cortex and the hippocampus. These plastic changes include in some

instances a long-term increase (potentiation, LTP) in the efficacy of synaptic transmission (cf. Hopkins and Johnston, 1984, 1988; Huang and Kandel, 1996; Kirkwood *et al.*, 1999; Thomas *et al.*, 1996; Lin *et al.*, 2003). In particular, when the excitatory synapses are rapidly and repeatedly stimulated for brief periods (tetanic stimulations), the postsynaptic neurons generate action potentials more readily upon subsequent stimulation.

In other instances, however, a long-term decrease (depression, LTD) in the efficacy of synaptic transmission occurred (Dahl and Sarwey, 1989; Katsuki *et al.*, 1997; Kirkwood *et al.*, 1999; Scheiderer *et al.*, 2004). Quite relevant to memory processes are those plasticities-dependent events on postsynaptic  $\text{Ca}^{2+}$  entry through N-methyl-D aspartate, NMDA receptors (Malenka, 1999). In fact, NMDA receptors knock-out mice lack NMDA receptors-dependent LTP and perform poorly on spatial-memory tasks (Tonegawa *et al.*, 1996; Tsien *et al.*, 1996). Although there has been much focus on LTP and its relation to learning and memory, a growing literature suggests that LTD is also critical to cognitive function (cf. Nakao *et al.*, 2002; Baunewell and Manahan-Vaughan, 2001; Manahan-Vaughan and Braunewill, 1999; Scheiderer *et al.*, 2004 for ref.). It is of interest that NE which is released from LC afferents, modulate synaptic function via activation of G protein-coupled adrenergic receptors, including  $\alpha_1$ ,  $\alpha_2$  and  $\beta$ -receptors (cf. Scheiderer *et al.*, 2004 for ref.). Studies with cell cultures (Lin *et al.*, 1998) and transgenic mice (Thome *et al.*, 2000) have shown that NE can stimulate gene transcription by increasing the phosphorylation of CREB via activation of cAMP cascade and protein kinase A ( $\beta$ -adrenoceptors) and/or via activation of calcium-dependent protein kinases ( $\alpha_1$ -adrenoceptors).

As reported by Berridge and Waterhouse (2003), LTP may involve either the MF input to CA 3 of the hippocampus (from the dentate gyrus), or the Schaffer collateral input to CA 1 (from the entorhinal cortex), or the perforant path input to the dentate gyrus. Interactions between the noradrenergic system and synaptic plasticity are well documented and their possible participation in memory processing has been underlined by several investigators (Bramham *et al.*, 1997; Berridge and Foote, 1991; Brocher *et al.*, 1992; Hopkins and Johnston, 1988; Huang and Kandel, 1996; Jzumi and Zorumski, 1999; Katsuki *et al.*, 1997; Pelletier *et al.*, 1994; Thomas *et al.*, 1996). In particular, it appears that administration of NE during high frequency stimulation of the MF in the rat hippocampal slice *in vitro* produced a reversible increase in magnitude, duration and probability of induction of LTP in the CA 3 subfield (Hopkins and Johnston, 1984). It appeared also that the cyclic AMP and the cAMP-dependent protein kinase A are required in the MF pathway for both the early phase of LTP (Huang *et al.*,

1994, 1996; Weiskopf *et al.*, 1994) as well as for the protein synthesis-dependent late phase (Huang *et al.*, 1994, 1996). Several reports have also shown that a facilitation of tetanus-induced LTP could be elicited by NE through activation of  $\beta$ -adrenergic receptors (Hopkins and Johnston, 1988; Huang and Kandel, 1996; Thomas *et al.*, 1996; Froehring *et al.*, 1989; Lin *et al.*, 2003), with fewer studies examining a modulatory effect of NE on LTD induced by low frequency stimulation (Dahl and Sarvey, 1989; Katsuki *et al.*, 1997; Kirkwood *et al.*, 1999; Scheiderer *et al.*, 2004). It should also be mentioned that after activation of  $\alpha_1$  adrenergic receptors by NE, a LTD of glutamate transmission has been observed not only in slices of visual cortex (Kirkwood *et al.*, 1999), but also in the rat hippocampal CA 3-CA 1 synapses (Scheiderer *et al.*, 2004). This LTD reported in forebrain structures possesses the characteristics of a Hebbian form of synaptic plasticity (Hebb, 1949), in that it requires coincident presynaptic activity and postsynaptic NMDA receptor activation. The finding that NE can induce LTD of glutamate transmission in hippocampus, as well as in visual cortex suggests that the NE-dependent form of synaptic modulation is a general mechanism by which the adrenergic system manipulates synaptic efficacy.

We have seen in Section 8 that heterosynaptic activation of P-cells in the cerebellar cortex increases the expression of IEGs such as c-Fos and Jun B and that when CF activation causes a high  $[Ca^{2+}]_i$ , the nuclear protein CREB is phosphorylated by the  $Ca^{2+}$  calmodulin-dependent protein kinase type IV (Ca MKIV), which may thus contribute to the late phase of LTD.

Experiments reported in Section 11 suggest that a waking state may occur during combined visual-vestibular or neck-vestibular stimulation which lead to adaptation of the VOR and the VSR respectively. It appears also that the increased discharge of LC neurons which occurs during this animal state may not only increase the responsiveness of the cerebellar P-cells to the multisensory stimuli, but also potentiate the plastic changes which affect different areas of the cerebellar cortex during vestibular adaptation (see Sections 4 and 6).

The importance of the noradrenergic system in brain plasticity is supported by the observation of Kasamatsu, Pettigrew and Ary (1981), who demonstrated that depletion of NE in kitten visual cortex by 6-hydroxydopamine (6-OHDA), the neurotoxin that destroyed the noradrenergic terminals, abolished the ocular dominance plasticity (cf. also Kasamatsu and Pettigrew, 1976, 1979), which, however, was enhanced by microperfusion of the visual cortex with NE. In particular, this agent accelerated the recovery of binocularly cortical cells from the effects of brief monocular visual deprivation (cf. also Kuppermann and Kasamatsu, 1984; Imamura and Kasamatsu, 1988, 1991). Infusion of  $\beta$ -adren-

ergic antagonists (propranolol, sotalol and metoprolol) in kitten visual cortex blocked the action of NE (Kasamatsu and Shirokawa, 1985; Shirokawa and Kasamatsu, 1986, 1987; Shirokawa *et al.*, 1989), indicating that activation of  $\beta_1$  receptors is mostly involved in the regulation of ocular dominance plasticity (Kasamatsu and Shirokawa, 1985, 1986; Shirokawa and Kasamatsu, 1986).

In another study, the  $\alpha_2$  receptor agonist clonidine was used to decrease NE release from presynaptic terminals and this was also found to reduce the ocular dominance plasticity (Nelson *et al.*, 1985). Experiments of unilateral lesion of the LC have finally shown the important role of NE in plastic events occurring in the somatosensory cortex of adult rat (Levin *et al.*, 1988).

*In vitro* slice experiments have provided evidence that NE facilitates cortical synaptic plasticity through a NMDA receptor-modified response mechanism (Brocher *et al.*, 1992; Kirkwood *et al.*, 1999). In particular, NE could increase the probability of activation of NMDA receptors by its action on membrane  $K^+$  conductance and second messengers. It has been shown that NE, through  $\beta$  receptors, reduces various  $K^+$  conductances in cortical neurons (Froehring *et al.*, 1989). Reduction of  $K^+$  conductances, in turn, increases the amplitude of depolarizing synaptic response, and thus may facilitate excitatory input to reach the threshold of synaptic modifications. NE can also increase intracellular levels of cAMP through activation of  $\beta$ -receptors and hence influence the activity of cAMP-dependent protein kinase A, which may have synergistic interactions with down-stream responses induced by NMDA receptor activation. Evidence for an involvement of the second messenger cAMP in ocular dominance plasticity and his action on protein kinase A has been reported by Gu (2002). In addition pharmacological inhibition of protein kinase A, where activity depends on cAMP, blocked ocular dominance shifts following monocular deprivation in kitten visual cortex (Beaver *et al.*, 2001).

### SECTION 13. RESPONSES OF NORADRENERGIC LC NEURONS TO GRAVITY CHANGES DURING THE SPACE FLIGHT

Pompeiano and his research group were competitively selected by the Committee of Molecular and Cellular Biology of the NIH to participate in the NASA Spacelab Mission Neurolab (STS-90), which occurred in April 1998, examining the "effects of gravity changes on gene expression in the brain of rats". They investigated in this animal species the effects that different gravitational conditions exert on the induction of immediate early genes (IEGs) in the

CNS (Pompeiano *et al.*, 2003). In particular, immunocytochemical methods were used to detect in different brain structures Fos and FRA (fos-related antigen) proteins, which encode for the transcription of factors that control the expression of several target genes (Herdegen and Leah, 1998; Morgan and Curran, 1991; Clayton, 2000). While Fos levels peak within 2 hours after stimulus exposure, and return to baseline values within 6-8h, FRA levels peak later and persist in the brain for days and weeks after the initial stimulus (Nestler *et al.*, 1999). Fos and FRA may thus contribute to *short-lasting* and *long-lasting* regulations of brain functions, respectively. Changes in Fos and FRA expression were evaluated in most of the brain structures, which are potentially involved in the adaptation of relevant functions following exposure to gravity changes during the space flight (cf. Pompeiano *et al.*, 2003).

The main result of these experiments was that an increased expression in Fos and FRA proteins occurred in the LC, particularly when the gravity force increased at the reentry (Pompeiano M. *et al.*, 2002). This finding was also associated with a parallel increase in Fos and FRA expression in the nucleus paragigantocellularis lateralis, a structure which in ground-based experiments exerts a direct excitatory influence on the noradrenergic LC neurons (cf. for ref. d'Ascanio *et al.*, 2002).

The increase in gene expression which affected the LC did not depend only upon the increase in the gravity force at the reentry, but was also associated with a state of active waking and/or stress, as shown by the occurrence of an increase in Fos and FRA expression which occurred in different areas of the neocortex as well as of the hippocampus during this phase of the space flight (Pompeiano *et al.*, 2003; Centini *et al.*, 2006). These are actually the structures which undergo an increase in gene expression during the waking state occurring in ground-based experiments. These findings are quite relevant to the observation by Wilson and McNaughton (1993) and Knierm *et al.*, (2000), who found that these structures, particularly the hippocampus, play a prominent role in spatial orientation and memory.

In addition to the LC and the forebrain structures indicated above, Fos and FRA expression occurred also in the superior and medial vestibular nuclei, which are known to contribute to the VOR, as well as in the spinal vestibular nucleus, but not in the lateral vestibular nucleus of Deiters, which contributes to the VSR (Pompeiano *et al.*, 2002). No attempt was made to evaluate the changes in gene expression which affected the cerebellar cortex during the space flight, since this structure was not attributed by the NASA to our team. However, a prominent increase in Fos and FRA expression was found in the vestibular and visual areas

of the inferior olive (IO), i.e. in those structures which are involved in the VOR adaptation, such as the dorsomedial cell column, the  $\beta$  subnucleus and the dorsal cap of Kooy of the medial nucleus (d'Ascanio *et al.*, 2003). These were actually the olivary regions which showed glucose utilization in ground-based experiments performed in cats after slow sinusoidal roll tilt of the animal with parameters leading to selective stimulation of macular receptors (as studied by [14C]-2-deoxyglucose autoradiography) (d'Ascanio *et al.*, 1981; see also Fig. 125 cf. Ito, 1984). Even in these instances, the increase in gene expression reported above occurred particularly during exposure of the animal to the *gravity* force at the reentry (d'Ascanio *et al.*, 2003). It is of interest that during the space flight a gene expression affected also the subnuclei A, B, C and the caudal part of the medial IO, which receive spinal afferents, but this effect occurred only during exposure of the rat to *microgravity*, as shown 1 day and 12 days after launch.

Since most of the structures indicated above receive noradrenergic afferents from the LC (see Foote *et al.*, 1983), we postulated that the LC neurons may induce gene expression in most of their target neurons (such as the vestibular area of the IO, and some of the vestibular nuclei). In agreement with this hypothesis was the fact that an increase in Fos and FRA expression affected at the reentry also autonomic areas of the medulla, such as the NTS (nucleus of the tractus solitarius), and the area postrema (a structure involved in space motion sickness), as well as in the central nucleus of the amygdala (Pompeiano *et al.*, 2004), a structure involved in the processing of emotions, as well as in the expression of fear and anxiety. All these structures receive noradrenergic afferents (cf. for ref. Foote *et al.*, 1983; Barnes and Pompeiano, 1991).

The demonstration that an increase in gene expression affected both the NTS and the central nucleus of the amygdala, which control autonomic functions, led us to postulate that the increase in active waking which occurred at the reentry was also associated to a condition of stress (cf. Pompeiano M. *et al.*, 2002). The demonstration that most of the structures which undergo an increase in Fos and FRA expression at the reentry, as reported above, receive noradrenergic afferents from the LC indicates that all these projections determine a sustained induction of IEGs in their target structures, during the appropriate phase of the space flight. It should also be mentioned that Fos and FRA expression which occurred in the activated LC neurons at the reentry may regulate in these neurons the expression of tyrosine hydroxylase, the rate-limiting enzyme involved in the NE synthesis (Gizang-Ginsberg and Ziff, 1990). Thus the activation of LC neurons may determine the induction of IEGs in their target structures,

which would be sustained during and after the reentry. As indicated above, the induced changes in gene expression so far described may be functionally important to determine not only the adaptive changes which occur during the space flight after exposure of the animal to about 0G, but also the changes which occur at the reentry during readaptation to the terrestrial environment (1G).

#### SECTION 14. POSSIBLE ROLE OF THE EFFERENT (EVe) NUCLEUS IN VESTIBULAR ADAPTATION DURING THE SPACE FLIGHT

An additional structure which undergoes changes in gene expression during the space flight is represented by the efferent vestibular (EVe) nucleus, a site located dorsolateral to the facial genu and ventromedial to the medial vestibular nucleus (Goldberg *et al.*, 2000). This structure sends *efferent fibers* to sensory hair cells, particularly to type II hair cells located in both the maculae and the cristae, thus contributing to centrifugal influences on sensory receptors and their afferents (cf. Wersäll, 1972).

Rats exposed to microgravity showed a significant *decrease* in number of cells expressing Fos and FRA proteins in the EVE nucleus within 1 day after launch, i.e. when the gravitational force decreased to about 0 G, a finding which was maintained for at least 12 days in space. This change disappeared 1 day after return to earth and spaceflight subjects maintained normal numbers of IEG expressing cells for at least 14 days after landing (Balaban *et al.*, 2002). Electrophysiological observations by Boyle *et al.* (2001) supported these findings. Ross (1993, 1994, 2000; Ross and Vardas, 2003) had previously examined in adult rats hair cells and their ribbon synapses in a transmission electron microscope and found that the number of utricular (and saccular) hair cell synapses increased significantly in both type I and type II hair cells within 24 hrs after launch, but declined to near baseline values 12 days after launch. This finding, which was attributed to *functional deafferentation*, indicates that synaptic plasticity occurs rapidly in weightlessness. Our observation with Balaban *et al.*, (2002) add the important notion that *changes in the centrifugal control to type II hair cells and their afferents* may contribute to the observed synaptic alterations.

The vestibular efferent neurons located in the EVE nucleus project not only to the labyrinths, but also send collateral projections to the flocculus (and ventral paraflocculus) bilaterally (Shinder *et al.*, 2001), i.e. to structures involved in the VOR adaptation. The persistence times of Fos and FRA protein expres-

sion (hours and days, respectively, cf. Nestler *et al.*, 1999) in the EVe nucleus suggest that their neurons are likely to be involved in both short-term and long-term plastic changes which affect the dynamic sensitivity of vestibular afferent neurons to angular and linear acceleration during exposure to microgravity and at the reentry. The possibility also exists that the same neurons intervene in the modulation of activity of both the secondary vestibular neurons and the related P-cells during the VOR adaptation. This hypothesis, if confirmed, could be related to that by Miles and Lisberger (1981), i.e. that *vestibular brainstem plasticity* contributes with *cerebellar plasticity* to determine appropriate amounts of VOR adaptation (see Section 5). Our findings suggest that these adaptive changes may vary during exposure to altered gravitational environment.

#### SECTION 15. EFFECTS OF UNILATERAL LABYRINTHECTOMY (UL) ON GENE EXPRESSION IN THE LC AND RELATED STRUCTURES

The hypothesis that noradrenergic LC neurons exert a prominent role in gene expression during the gravity changes related to the space flight is supported by the results of lesion experiments following unilateral labyrinthectomy (UL). Experiments performed by Cirelli *et al.*, (1996a) have *originally* shown that unilateral labyrinthectomized rats undergo asymmetric changes in c-Fos mRNA and the related Fos-protein in the LC of both sides, which increase mainly on the intact side. These Fos-positive LC neurons were noradrenergic in nature, as they could be double-labeled by combining Fos-protein immunocytochemistry with the immunocytochemical detection of tyrosine hydroxylase (d'Ascanio *et al.*, 1998a, b, 2000). This finding appeared already 3h after UL and disappeared after 24h, when partial compensation of the vestibular syndrome had occurred. In the same experiments, an asymmetric increase of c-fos and/or Fos protein expression occurred also in the vestibular nuclei, the cerebellar cortex, the inferior olive and the caudate-putamen. Thus the asymmetric labyrinthine signals following UL could drive not only the noradrenergic LC system, but also some of the related cerebellar and brain targets, where the increase in Fos expression may determine the plastic changes which are responsible for vestibular compensation. In particular, we postulated that activity in the inferior olive (IO) of the intact side, following UL, may through the crossed olivo-cerebellar system induce a local depolarization of the unmyelinated noradrenergic nerve terminals which surround particularly the P-cells of the cerebellar cortex of the lesioned

side, thus leading to a local release of NE (*see Section 9*). This agent would then trigger the molecular changes which may contribute to vestibular compensation (*see Section 12*).

#### SUMMARY

1) The inhibitory influence that the Purkinje (P)-cells exert on lateral vestibular (Deiters') and cerebellar nuclei neurons was originally shown in experiments of *extracellular* unit recording (De Vito *et al.*, 1956; Pompeiano and Cotti, 1959; Arduini and Pompeiano, 1957). This finding was confirmed by Ito (1966, 1970) who adds the important notion, i. e. that this inhibitory influence is *monosynaptic* in nature, as shown by experiments of *intracellular* unit recording (Section 1).

2) These findings associated with the discovery by Lund and Pompeiano (1968) that the lateral vestibular nucleus (of Deiters) exerts a direct *monosynaptic* excitatory influence on limb extensor motoneurons, support their conclusion, that the postural atonia following stimulation of the cerebellar anterior vermis is not due to fastigial activation of the medullary inhibitory reticulospinal neurons, but rather to suppression of the excitatory influences that lateral vestibulospinal (VS) neurons exert on extensor motoneurons (Section 2).

3) In analogy with the three-neuronal vestibulo-ocular reflex (VOR) arc, originally described by Lorente de Nó (1933), Lund and Pompeiano (1968) describe a three-neuronal vestibulospinal reflex (VSR) arc, made by primary vestibular afferents, lateral VS neurons and spinal extensor motoneurons. Ito discovered that the flocculus P-cells act out-of-phase with respect to the vestibulo-oculomotor neurons, thus exerting a positive influence on the basic VOR. Experiments performed in our laboratory have shown that P-cells in the zone B of the cerebellar anterior vermis, which project to Deiters nucleus (Corvaja and Pompeiano, 1979), undergo a modulation of their simple spike discharge (Denoth *et al.*, 1979, 1980) during roll tilt of the animal, which was opposite in phase with respect to that of lateral VS neurons (Boyle and Pompeiano, 1981; Marchand *et al.*, 1987), thus duplicating the anatomo-functional organization that the cerebellar flocculus exerts on the VOR (Section 3).

4) Ito *et al.* (1974) described in rabbits the phenomenon of the VOR adaptation, a finding which confirms the original observation previously performed in *humans* by Gonshor and Melvill Jones (1971). Ito *et al.* were the first, however, to demonstrate that in animal experiments flocculectomy decreased or suppressed the adaptive changes which affected the horizontal VOR. Ito and

Miyashita (1975) also observed that interruption of the climbing fiber (CF) input to the flocculus replicated the effects of the flocculectomy (Section 4).

5) Ito's (1982) hypothesis that the flocculus P-cells adaptively controls the VOR gain by regulating the signal flow from the labyrinth to the relay cells of the VOR was challenged by Miles and Lisberger (1981), who postulated that plastic changes actually occur in flocculus target neurons, i.e. in the vestibular nuclei, which may thus contribute to the VOR adaptation. In spite of the controversies between the Japanese and American followings, discussed in detail both by Ito and Lisberger and Sernowsky (1993), it appears that the results obtained by the two groups of researchers were/are partly correct, the flocculus playing an important role in the *induction* of adaptation, while the vestibular nuclei to which the flocculus sends its efferents being the site of the *retention*. The conclusion of our review, i.e., that there are multiple sites for modifiable synapses in both the cerebellum and the vestibular nuclei, may thus integrate the original observation by Ito, who postulated that plasticity occurred only in the cerebellar cortex of the flocculus (Section 5).

6) Ito (1982, 1984) postulated on theoretical ground that only the VOR, which represents a feed-forward control system lacking feed-back from output to input, requires assistance from the cerebellum. On the other hand, the VSR, which represents a typical closed-loop control system equipped with an efficient feed-back from the output to the input, does not require assistance from the cerebellum. This conclusion was modified experimentally by Pompeiano and his group, who demonstrated that the somatosensory inputs to the cerebellar vermis originating either from the neck (Andre *et al.*, 1993) or from the wrist (Manzoni *et al.*, 2004) may transmit "error signals" which lead to an adaptive increase in gain of the VSR during combined neck-vestibular or forepaw-vestibular stimulation. These somatosensory signals projecting to the cerebellar anterior vermis may utilize CF, in analogy with the visual signals which project to the cerebellar flocculus and lead to an adaptive increase in gain of the VOR during combined visual-vestibular stimulation. Experiments of functional inactivation of the zone B of the cerebellar anterior vermis indicate that this corticocerebellar area represents an inhibitory side-loop of the VSR pathway (Manzoni *et al.*, 1994), in the same way as the flocculus has been viewed by Ito as an inhibitory side-loop of the VOR pathway (cf. also van Neerven *et al.*, 1989) (Section 6).

7) Ito *et al.* (1982, cf. also Ito, 1989, 2001, 2002) studied the biochemical and the cellular basis of the VOR adaptation. In this respect, they followed the earlier theoretical proposal by Marr (1969), who postulated that simultaneous sig-

nals arriving at the cerebellar cortex through parallel fibers (PF) and climbing fibers (CF) produce a desensitization of the excitatory responses made by parallel fibers on P-cell dendrites (or LTD), thus leading to an adaptive increase in gain of the VOR. The metabolic chains involved in regulating synaptic transmission to P-cells and leading to desensitization of glutamate receptors at the parallel fiber synapse on P-cell dendrites showed unexpected complexities. In particular, it appears that  $\text{Ca}^{2+}$  entry in the P-cell dendrites during the CF impulses triggers intracellular enzyme reactions, which could play roles in facilitating desensitization of glutamate receptors. Cerebellar P-cells are rich in cyclic GMP-dependent protein kinase type I (cGKI or PKG) and its specific G-substrate. It appears, also, that protein kinases and phosphatases acting together regulate the level of phosphorylation of proteins including synaptic receptors. When phosphorylated by PKG, G substrate acts to inhibit protein phosphatases. In addition to PKG, P cells also contain cyclic AMP-dependent protein kinase (PKA) and protein kinase C (PKC). The sustained desensitization of the excitatory responses made by the parallel fibers on P-cell dendrites affects specifically the ionotropic (AMPA) glutamate receptors. Conjunctive application of AMPA and 8-Br-cGMP to cerebellar slice (i.e. *in vitro*) mimicking heterosynaptic activation of P-cells causes a desensitized state which may promote the synaptic LTD. It appears also that group I metabotropic glutamate receptors activation triggers a chain of reactions which contribute to activation of cGMP-dependent protein kinase (PKG), eventually affecting AMPA receptors (Ito and Karachot, 1990a, b) (Section 7).

8) After the demonstration that LTD was due to desensitization of glutamate receptors on P cells, *in situ* hybridization and immunohistochemical techniques were used to study the expression of immediate early genes (IEGs) following the synaptic LTD produced by different modalities of stimulation of CF and axons of granule cells (Nakazawa *et al.*, 1993; Yamamori *et al.*, 1999). They report that an increase in local induction of *c-fos* and *Jun-B* occurred in P-cells. Both these IEGs forms an heterodimer transcriptional factor, called AP-1 complex, the protein products of which may function as third messengers, to regulate the transcription of target genes. These genes may represent the neuronal mechanism by which short-term signals at the cell membrane are transduced into long-term biochemical changes to transynaptic signals that are required for cerebellar long-term plasticity. The cyclic AMP response element-binding protein (CREB) is a nuclear protein regulating the transcription of genes with a CRE site in their promoter. When synaptic activation causes a high  $[\text{Ca}^{2+}]_i$ , CREB is phosphorylated at its transcriptional regulatory residue (serine-133) by

involving the  $\text{Ca}^{2+}$ -calmodulin-dependent protein kinase type IV (CaMK IV). There is now evidence that both CREB and CaMK IV contribute to the late phase of LTD, a mechanism that weakens the neurotransmission of excitatory synapses made by parallel fibers on target neurons (Ahn *et al.*, 1999; Ho *et al.*, 2000) (Section 8).

9) An interesting comment advanced by Ito (1984, p. 127) was that glutamate receptors may not necessarily be stimulated by neurotransmitter release from parallel fibers (PF), if they are located remote from PF-P-cell synapses. He postulated that CF release an unknown chemical substance which may react with both subsynaptic receptor molecules and/or parallel fiber neurotransmitter. The nature of this substance, however, was not identified. It is known that CF activation of P-cells is associated not only with an increased *intracellular* concentration of  $\text{Ca}^{2+}$ , but also with a significant increase of *extracellular*  $\text{K}^+$  concentration, due to movement of  $\text{K}^+$  ions out of P-cell dendrites during depolarization-dependent and  $\text{Ca}^{2+}$  dependent increase of the membrane  $\text{K}^+$  conductance (Stöckle and ten Bruggencate 1980). We postulated (d'Ascanio *et al.*, 1998a) that these ionic changes induced a local depolarization of the noradrenergic *unmyelinated* nerve terminals which surround the P-cell dendrites, thus leading to release of norepinephrine (NE). Since the P-cell somata are surrounded by  $\beta$ -adrenergic receptors ( $\beta\text{AR}$ ) (Altas *et al.*, 1977), we hypothesized that NE could play a prominent role in the induction of the long-term plastic changes which are at the basis of the vestibular adaptation and that these effects were mediated through  $\beta\text{AR}$  (Perkins *et al.*, 1990).

Van Neerven *et al.*, (1990) discovered that intrafloccular microinjection in adult belted rabbits of a  $\beta$ -adrenergic agonist or antagonist increased or decreased, respectively, the amplitude of the VOR adaptation occurring during sustained visuo-vestibular stimulation. Similarly, intravermal microinjection of  $\beta$ -adrenergic antagonists prevented in decerebrate cats the occurrence of the adaptive increase in gain of the VSR occurring during sustained neck-vestibular stimulation (Pompeiano *et al.*, 1994a, b). There is now evidence that the noradrenergic LC neurons act on corticocerebellar neurons through  $\beta$  activation of a cAMP-dependent mechanism, to increase c-fos and Jun B-expression which actually occurs during vestibular adaptation. Observations by Hausdorff *et al.* (1990) have shown that in rats brief exposure to NE or epinephrine of plasma membranes which included the  $\beta\text{AR}$ , the stimulatory guanine-nucleotide binding protein  $\text{G}_s$ , and the enzyme adenylylcyclase (AC), which catalyzes the formation of cAMP from ATP, results in profound increases in the intracellular concentration of the second messenger cAMP, which wane rapidly within a few

min despite continuous exposure of P-cells to these stimuli. The molecular mechanisms underlying this rapid  $\beta$ AR desensitization do not appear to require internalization of the AMPA receptors, but rather an alteration of the functioning of  $\beta$ AR themselves, that uncouples the receptors from the stimulatory G protein  $G_s$ . This uncoupling phenomenon involves the phosphorylation of  $\beta$ AR by at least two kinases, PKA and  $\beta$ AR Kinase ( $\beta$ ARK). The very rapid attenuation of the AC response elicited by a short-term exposure to agonists, disappears in min after removal of the desensitizing agonist and without a requirement for new protein synthesis. However, recovery from the profound desensitization induced by prolonged exposure to agonist requires new protein synthesis and may take hours or days (Section 9).

**10)** Electrophysiological experiments of unit recordings performed in decerebrate cats have shown that noradrenergic LC neurons responded to both static and dynamic stimulation of macular labyrinth receptors (Fung *et al.*, 1987; Manzoni *et al.*, 1989; Pompeiano *et al.*, 1990). The same neurons also responded to visual signals (Aston Jones and Bloom, 1981) and proprioceptive neck signals (Barnes *et al.*, 1989; Manzoni *et al.*, 1989). It is likely, therefore, that both the flocculus and the cerebellar anterior vermis receive noradrenergic signals not only through the local mechanism postulated above (Section 9), but also through a reflex activation of LC neurons during out-of-phase visuo-vestibular or proprioceptive neck-vestibular stimulations. (Sections 10).

**11)** Observations made in intact unanesthetized animals suggest that the sensory signals which are involved in the adaptation of the VOR and the VSR may also contribute to a waking state and that this state is likely to be associated with an increased discharge of the LC neurons (cf. Hobson and Steriade, 1986). There is also evidence that this increased discharge of noradrenergic LC neurons, determines the induction of IEG in several target structures. In particular, it appeared that IEGs encoding c-fos and nerve growth factor induced A, NGFI-A, increased in the cerebral cortex and the hippocampus during waking (Pompeiano M. *et al.*, 1994). An important pathway, by which NE release during waking may facilitate the induction of IEGs in ground-based experiments by acting through  $\beta$ AR, involves the phosphorylation of the cAMP response element-binding protein (P-CREB), which can act on the promoters for c-Fos and NGFI-A. Unilateral injection in the LC of rats of 6-OHDA, a neurotoxin that destroys catecholaminergic neurons, decreases the concentration not only of Fos and NGFI-A, but also of P-CREB in cortical areas depleted of noradrenergic fibers (Cirelli, Pompeiano M. and Tononi, 1996). Given the similar distrib-

utions of Fos expression during waking and of  $\beta$ -noradrenergic receptors into the cerebral cortex, it has been suggested that NE released by LC terminals during waking may induce Fos by acting through a pathway that leads from  $\beta$ AR to CREB phosphorylation (Section 11).

**12)** The noradrenergic LC neurons induce various forms of activity-dependent synaptic plasticity not only in the cerebellar cortex, but also in the cerebral cortex and the hippocampus. Specific forms of synaptic plasticity induce in some instances a long-term increase (potentiation, LTP) or a long-term decrease (depression, LTD) in the efficacy of synaptic transmission, which are quite relevant to learning and memory. Evidence was also presented indicating that a facilitation of tetanus-induced LTP could be elicited by NE through activation of  $\beta$ AR (Hopkins and Johnson, 1988; Huang and Kandel, 1996; Thomas *et al.*, 1996; Kirkwood *et al.*, 1999; Lin *et al.*, 2003). The importance of the noradrenergic system in brain plasticity is supported by the results of previous observations showing that in kittens the noradrenergic system intervenes in the ocular dominance plasticity (Kasamatsu and Pettigrew, 1976, 1979) and that this effect is mediated through  $\beta$ -adrenoceptors (Kasamatsu and Shirokawa, 1985, 1986) (Section 12).

**13)** Pompeiano *et al.* (2003) have investigated during the NASA Neurolab mission (STS90) the response of noradrenergic LC neurons and related structures to gravity changes during the space flight. In particular, they found that in rats an increased expression in Fos and FRA proteins occurred in the LC when the gravity force increased at the reentry (Pompeiano M. *et al.*, 2002). This finding was also associated with a parallel increase in Fos and FRA expression in the nucleus paragigantocellularis lateralis, a structure which exerts a direct excitatory influence in the noradrenergic LC neurons (cf. d'Ascanio *et al.*, 2002). An increase in Fos and FRA expression also affected the superior and medial vestibular nuclei, which contribute to the VOR, but not the lateral vestibular nuclei, which contribute to the VSR (Pompeiano *et al.*, 2002). A prominent increase in Fos and FRA expression also occurred in the vestibular and visual areas of the inferior olive, i.e. in structures such as the dorso-medial cell column, the  $\beta$  subnucleus and the dorsal cap, which are involved in the VOR adaptation (d'Ascanio *et al.*, 2003). A prominent increase in Fos and FRA expression also affected the NTS (nucleus of the tractus solitarius) and the central nucleus of the amygdala, which control autonomic functions and are likely to be associated to a condition of stress (Pompeiano *et al.*, 2004). The demonstration that most of the structures which undergo an increase in Fos and FRA expression at the reentry receive noradrenergic afferents from the LC indicates

that these projections determine a sustained induction of IEGs in their target structures during this appropriate phase of the space flight (Section 13).

**14)** Further observations made in rats have shown that neurons located in the efferent vestibular nucleus (EVe), a structure located ventromedial to the medial vestibular nucleus (Goldberg *et al.*, 2000), send efferent fibers not only: 1) to type II hair cells located in both the maculae and the cristae of both sides, which contribute to centrifugal influences on sensory receptors and their afferents (Wersäll, 1972), but also 2) to the cerebellar flocculus, which is involved in the VOR adaptation (Shinder *et al.*, 2001). Exposure of rats to microgravity produced a significant decrease in number of cells expressing Fos and FRA proteins in the EVe nucleus within 1 day after launch, a finding which disappeared soon after return of the animals to earth (Balaban *et al.*, 2002). The different persistence times of Fos and FRA proteins expression (hours and days, respectively) (cf. Nestler *et al.*, 1999) suggest that their neurons are involved in both the short-term and the long-term plastic changes which may affect not only the dynamic sensitivity of vestibular afferent neurons to angular and linear acceleration, but also intervene in the modulation of activity of both the secondary vestibular neurons and the related P-cells during the VOR adaptation (Section 14).

**15)** Cirelli *et al.*, (1996a) have finally studied the effects of unilateral labyrinthectomy (UL) on gene expression in the LC and found that in rats this lesion produced an asymmetric increase in Fos expression which affected not only the noradrenergic LC nuclei, but also the related structures located in the vestibular nuclei, the cerebellar cortex, inferior olive and caudate-putamen (Section 15).

**Abbreviations**

|            |                                                               |
|------------|---------------------------------------------------------------|
| AC         | adenylylcyclase                                               |
| ATP        | adenosintriphosphate                                          |
| $\beta$ AR | $\beta$ -adrenergic receptors membrane                        |
| cAMP       | cyclic adenosine monophosphate                                |
| CaMKIV     | $\text{Ca}^{2+}$ -calmodulin-dependent protein kinase type IV |
| CF         | climbing fibers                                               |
| CNS        | central nervous system                                        |
| CREB       | cAMP response element-binding protein                         |
| CS         | coeruleospinal                                                |
| EEG        | electroencephalogram                                          |
| EVe        | efferent vestibular nucleus                                   |
| FRA        | Fos-related antigen                                           |
| FTN        | flocculus target neurons                                      |
| IEGs       | immediate early genes                                         |
| IO         | inferior olive                                                |
| IPSPs      | inhibitory postsynaptic potentials                            |
| LC         | locus coeruleus                                               |
| LTD        | long term depression                                          |
| LTP        | long term potentiation                                        |
| LVN        | lateral vestibular nucleus of Deiters                         |
| MF         | mossy fibers                                                  |
| MVN        | medial vestibular nucleus                                     |
| NE         | norepinephrine                                                |
| NO         | nitric oxide                                                  |
| NOS        | nitric oxide synthase                                         |
| NTS        | nucleus of the tractus solitarius                             |
| 6-OHDA     | 6-hydroxydopamine                                             |
| OKR        | optokinetic reflex                                            |
| 2PDKCs     | two porw domaine potassium channels                           |
| P-cells    | Purkinje cells                                                |
| PF         | parallel fibers                                               |
| QA         | quisqualate                                                   |
| RS         | reticulospinal                                                |
| TB         | triceps brachii                                               |
| UL         | unilateral labyrinthectomy                                    |
| VN         | vestibular nuclei                                             |

VOR vestibulo-ocular reflex

VS vestibulospinal

VSR vestibulospinal reflex

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