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VESTIBULAR COMPENSATION IS AFFECTED BY TREATMENT WITH DOPAMINE ACTIVE AGENTS

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INTRODUCTION

Hemilabyrinthectomy (HL) is followed by a wide range of postural, locomotor and ocular symptoms which disappear over a precise time course. This recovery process, usually called vestibular compensation, is characterized by several metabolic, anatomical and neurochemical events, that take place in the central networks of sensorimotor systems, involving vestibular, visual and somatosensory centers (20). It can be regarded as a good experimental model for the study of adaptive learning, based on neuroplasticity mechanisms, changes in synaptic efficacy and substitution processes (28).

Compensation time course can be influenced by experimental manipulations and the effectiveness of various pharmacological agents in promoting repair capacities has been extensively tested. Different classes of drugs are capable of affecting the vestibular response to injury (17). Conceptually, one can classify drugs as to whether they accelerate or retard compensation, or produce decompensation or overcompensation. Drugs with sedative action (phenobarbital, alcohol, chlorpromazine, diazepam) are reported to slow down the reachievement of a symmetrical posture and motility, while excitatory agents (caffeine, ACTH, amphetamine) faster abate vestibular deficits that follow HL (17). These drugs are assumed to act aspecifically, by altering CNS activity level either by depressing or enhancing it. More focused pharmacological investigations have shown that the compensated state, when compared with the normal one, is characterized by an altered sensitivity towards drugs that act on central synapses (22). Thus, the study of pharmacological actions specifically interfering with the vestibular response to an injury, is intricately bound up with the knowledge of the synaptic events in intact as well as in compensated state.

Over the last decade, data concerning the identity and function of neurotransmitters in vestibular circuitry have been increased. Cholinergic, glutamatergic and GABAergic receptors are present within vestibular nuclei (11, 26), suggesting a role of these neurochemical systems in basic vestibular function and probably during vestibular compensation. It has been demonstrated that the compensated state is susceptible to the administration of agonists or antagonists of cholinergic (1, 5, 11) and GABAergic (5) receptors. Moreover, more recently it has been

proposed that a denervation supersensitivity of excitatory aminoacid receptors, namely the glutamate NMDA receptors, of the deafferented vestibular neurons could play a role in vestibular compensation (21, 25). A possible interpretation of these data is that vestibular recovery is obtained through a postsynaptic sensitivity of deafferented vestibular neurons different from that of vestibular neurons of the intact side.

As for monoamine systems, histochemical studies have evidenced serotonergic innervation of the vestibular complex (23), and electrophysiological data have shown that lateral vestibular neurons undergo excitation or inhibition following microiontophoretic application of serotonin (15). Conversely, no data are available in literature on the presence of a dopaminergic innervation of vestibular neurons. And yet, to dopaminergic transmission is attributed a relevant role in motor function as well as in learning and memory processes (4). Because of this dual role for dopamine (DA) and of the fact that vestibular compensation is a form of motor learning (28), the time course of recovery from vestibular deficits could be altered by a pharmacological treatment with DA agonists and antagonists.

The aim of the present study was to investigate the effects of post-operative administration of bromocriptine (a potent D_2 agonist), sulpiride (one of the most selective D_2 antagonist) or lisuride (an agent active on monoamine receptors, with a facilitatory effect on D_2 receptors) on functional compensation of postural and ocular symptoms in hemilabyrinthectomized guinea pigs.

METHODS

Guinea pigs (300-450 g) (n = 25) were used in the present study. Under ketamine (Ketalar, Parke-Davis, 35 mg/kg i.m.) and diazepam (Valium, Roche, 0.4 mg/kg i.m.) anaesthesia, the middle ear of the right side was opened and the labyrinth destroyed by drilling through the ampullae of the anterior and lateral semicircular canals. The opening was extended through the ampullo-utricular duct to destroy both the ampulla of the posterior semicircular canal and the utricle and saccule. Furthermore, in those animals in which ocular motility had planned to be recorded, a pair of head-restraining screws was cemented to the skull.

Each animal was randomly assigned to one of the four experimental groups. After the appearance of HL symptoms, the animals received the first of daily intraperitoneal injections of bromocriptine or sulpiride or lisuride, or of physiological saline. The Bromocriptine group (B-group, n = 7) was given 1 mg/kg bromocriptine (Parlodel, Sandoz) dissolved in Ringer's solution. The Sulpiride group (S-group, n = 5) was given 10 mg/kg sulpiride (Championil, Vita Farmaceutici) dissolved in Ringer's solution. The Lisuride group (L-group, n = 6) was given 0.1 mg/kg lisuride (Dobergin, Schering) in Ringer's solution. The control group (C-group, n = 7) was given Ringer's solution containing no drugs. The treatments lasted 21 days, beginning the day of the vestibular lesion which is later referred to as day 1.

Evaluation of postural asymmetries. — To evaluate postural asymmetries, a behavioural rating scale was built up taking into account the following symptoms: head deviation, head tilt, trunk curvature, forelimb extension, circling behaviour, righting reflexes from left and right lateral decubitus and finally rolling movements. A score ranging from 0 to 2 was assigned to each symptom according to its degree of severity. Thus the total

score ranged from 0 (absence of any asymmetry) to 16 (presence of all postural asymmetries to the highest degree). The scores were assigned during each of the 21 treatment days and successively up to the 48th post-operative day. All measurements were taken 1 h before i.p. injections to avoid eventual acute effects of drugs. The identity of specimens was unknown to the observer assigning them scores.

Recording of eye motility. — In 4 animals belonging to each experimental group, ocular asymmetries were evaluated, by recording spontaneous eye motility in the dark. Guinea pigs were restrained in a foam-rubber cradle. The head was securely fixed in a stereotaxic frame by means of the permanently implanted screws, taking care that the stereotaxic horizontal plane was the plane passing through the centres of the auditory canals and the inferior-most portion of the bone posterior to the incisors. The horizontal canals were brought into the earth horizontal plane by pitching the head 48° nose down. The movements of left eye were monitored with an infrared light projection technique (3). The cornea and conjunctiva were anaesthetized (Novesina, 0.4%, Wander) and a small suction cup bearing a light-emitting diode (LED) was attached. A photosensitive X-Y detector (United Detector Technology, SC250) gave a continuous X-Y indication of the incident centroid infrared light. The system was calibrated by moving the LED through known angular displacements. Horizontal and vertical eye positions were recorded on separate channels of a Grass polygraph. During the whole period of the recording the animals were kept in total darkness. Care was taken to maintain a constant arousal level by appropriate background noise. The spontaneous ocular motility was recorded at days 2, 7, 14, 21, 35 after the vestibular lesion.

Parameters of spontaneous ocular motility. — The parameters of spontaneous ocular motility taken into account were: the mean Slow Phase Eye Velocity (SPEV) for the horizontal (HSPEV) as well as the vertical (VSPEV) component; amplitude, duration and frequency of drifts. To distinguish among patterns of spontaneous drifts with similar mean velocities, but interspersed among differently lasting periods of holding of post-saccadic position, the ocular responses were analyzed by building up the Slow Cumulative Eye Position (SCEP) gained within 1-min samples. The SCEPs for the horizontal as well as the vertical component of eye motility were then combined together to derive the real oblique ocular trajectory of spontaneous drifts. The time courses of this DSCEP were evaluated.

Statistical analysis. — The results were first tested for homoscedasticity of variance and then comparisons among treated and control animals were made using «p x q» (group x time) analyses of variance for repeated measures within subjects. When the cell frequency was unequal, Winer's (27) model of «p x q» ANOVA with unequal cell frequency was used. When significant differences were found with the overall analyses, post-hoc comparisons between groups were assessed with Dunnett's multiple comparison test or Tukey's test.

RESULTS

1. *Recovery from postural asymmetries following hemilabyrinthectomy.* — In the HL animals belonging to all experimental groups, postural symptoms perfectly fitted with those previously described (18). Immediately after vestibular lesion on the right side, all animals exhibited a marked trunk curvature towards the injured side, head deviation in the horizontal plane towards the damaged labyrinth (yaw head tilt) as well as head torsion about the longitudinal axis towards the lesion side (roll head tilt). Moreover, a clear limb flexion ipsilaterally as well as a limb extension contralaterally to the lesion side were always present. Furthermore, the animals exhibited a severe impairment of righting reflexes from both lateral decubi-

ti, that in the very first days after the lesion brought to rolling movements around the body longitudinal axis with a corkscrew-like pattern. Finally, HL animals did not succeed in walking, showing a compulsive circling towards the lesion side, which prevented them from progressing in a straight line.

This acute stage was characterized by a rapid partial recovery from asymmetries. Fig. 1 illustrates the mean time courses of recovery from all postural asymmetries in the four experimental groups. As it is possible to note, different time courses of vestibular compensation were exhibited by the three treated groups when compared to controls.

To obtain a reliable estimate of the influence of treatments and of time, a 2-way repeated measure ANOVA was performed. The time points chosen for the analysis were 1, 4, 8, 12, 16, 20, 25 post-operative days. This statistical analysis revealed highly significant effects of treatments ($F_{(3,21)} = 10.68$; $p < 0.00033$) and time ($F_{(6,126)} = 372.88$; $p. < 0.00000$). Also interaction was significant ($F_{(18,126)} = 7.80$; $p < 0.00000$). A general look over of the time courses of compensation of all symptoms investigated in the three experimental groups treated with dopamine agonists or antagonists evidenced an accelerating effect of bromocriptine starting from the 4th post-operative day and lasting the whole period of compensation. Conversely, sulpiride significantly slowed down the time course of compensation, even if not altering the overall evolution of symptoms. The time course of compensation displayed by the animals treated with lisuride was the most delayed, reaching during the 21 days of drug treatment a sort of «freezing» of HL symptoms. Only when the treatment was over, the deficits exhibited a very slow abatement, not sufficient, however, to overcome the gap gained during the treatment period.

As vestibular compensation is a process encompassing a wide range of deficits compensated for to different degrees and with different time courses, it is seemed interesting to analyze the compensation time course of single HL symptoms in all experimental groups (Fig. 2; Table 1). B-group showed a significant effect of treatment as regards head torsion, head deviation, trunk curvature and righting reflexes from right decubitus.

S-group compensation significantly differed from controls as for the delayed

Table 1. — *Statistical comparisons of behavioral data in treated and control groups, made by «p x q» ANOVAs.*

	Treatment effect			Time effect			Interaction		
	Freedom degrees	F value	P	Freedom degrees	F value	P	Freedom degrees	F value	P
Head deviation	3,21	11.77	0.0002	6,126	42.34	0.00000	18,126	2.52	0.001
Head tilt	3,21	9.53	0.0005	7,147	8.20	0.00000	21,147	1.63	0.04
Trunk curvature	3,21	3.34	0.03	4,84	43.98	0.00000	12,84	2.37	0.01
Forelimb extension	3,21	9.94	0.0004	6,126	76.92	0.00000	18,126	2.98	0.0003
Right side righting	3,21	7.68	0.001	6,126	50.22	0.00000	18,126	1.21	n.s.
Left side righting	3,21	2.97	0.05	6,126	88.58	0.00000	18,126	0.97	n.s.

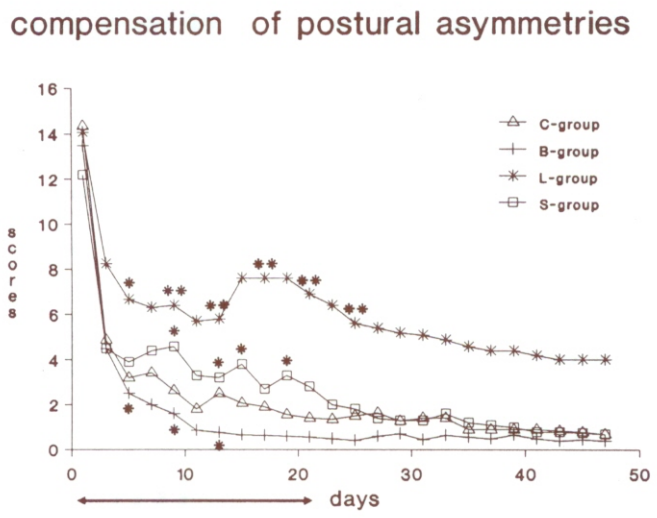

Fig. 1 – *Compensation of postural asymmetries in treated and control groups.*

The figure depicts the mean time courses of recovery from postural vestibular symptoms in treated and control animals.

Abscissa: time in days from hemilabyrinthectomy; ordinate: degree of severity of vestibular asymmetries evaluated according to the rating scale described in Methods. In this and in the following figures the thick horizontal bars indicate treatment period.

(* = $p < 0.05$; ** = $p < 0.01$, Dunnett's test).

recovery of a non-deviated head posture and of normal righting reflexes from right lateral decubitus.

Finally, L-group exhibited a striking delay in the recovery from all HL symptoms, particularly evident in the compensation of head tilt, head deviation as well as trunk curvature.

2. *Recovery from ocular asymmetries following HL.* — After the disappearance of vestibular eye nystagmus within the first 2-3 post-operative days, all HL animals were able to hold a stable ocular position in a lighted environment, even if the eyes displayed a tonic deviation: right eye (ipsilateral to lesion side) deviated downward and slightly backward, left eye deviated upward and slightly forward. Conversely, in the dark, the eyes drifted away from their resting position, then they were reset by a saccade in the opposite direction. Whenever the occurrence of resetting fast saccades combined in a regular pattern, the resulting ocular motility resembled a nystagmus modulation. These ocular asymmetries were by the time modified by compensatory mechanisms which tended to diminish ocular imbalance either by reducing the mean velocity of the drift or by prolonging the holding of post-saccadic eye position by diminishing the frequency of resetting fast phases.

Ocular drifts initially directed in the same direction of slow phase of the nystagmus, with time changed their trajectories either in the horizontal or in the vertical plane or in both. This shift, occurring more than once, led the eyes in the last recordings to drift in a direction opposite to the direction of slow phase of nystagmus immediately after the lesion (19).

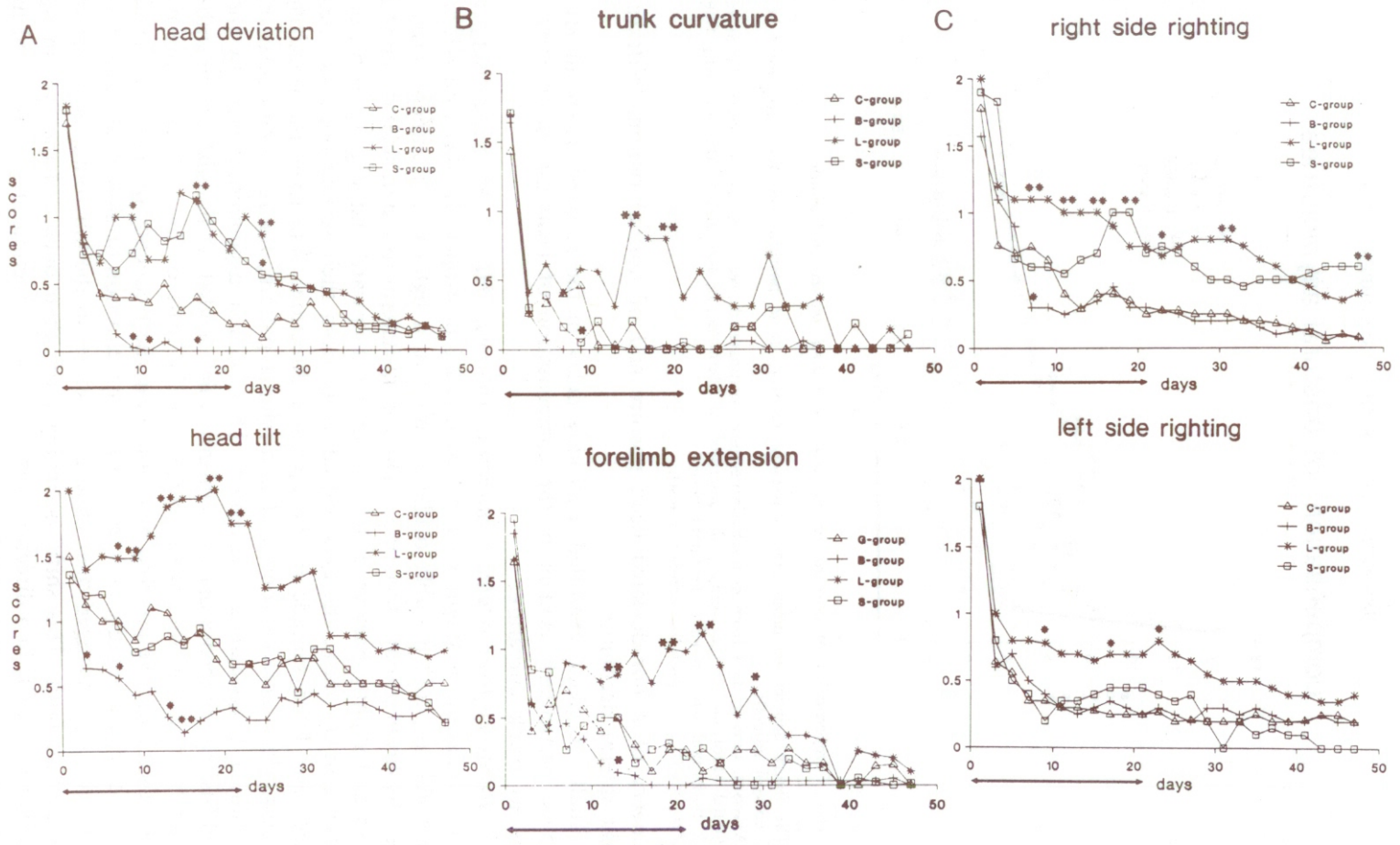
A
head deviation
B
trunk curvature
C
right side righting
head tilt
forelimb extension
left side righting
scores
days
C-group
B-group
L-group
S-group

Fig. 2

This picture was displayed by all experimental groups, but with clear differences in the slow phase eye velocity (SPEV) decay for horizontal as well as vertical components of spontaneous drifts (Fig. 3).

B-group exhibited an abatement of HSPEV similar to that of control group, except at the final recording in which treated animals displayed a slow phase eye velocity significantly higher than controls. As for vertical components, B-group showed a faster abatement of VSPEV, with respect to controls, reaching a stable vertical eye position by 21st post-operative day, while the control group displayed the same pattern of ocular stability by the 35th post-operative day. Conversely, a stable ocular position was never reached by L-group animals, either in the horizontal or in the vertical plane. Similarly, also in the S-group the time course of SPEV decay was significantly delayed respect to control group as regards horizontal as well as vertical components. A series of 4×5 (treatment $\times$ time) ANOVAs revealed significant effects of treatments and of time on compensatory rate of horizontal and vertical ocular asymmetries. Also interactions were significant (Table 2).

Fig. 4 shows the time course of evolution of DSCEP. It is possible to note that B-group exhibited a more stable ocular position with respect to controls during drug treatment, while when the drug treatment was over, it displayed an increase in ocular asymmetries. Conversely, the recovery from ocular asymmetries was significantly delayed in both L- and S-groups.

A further index of the extent of ocular compensation achieved by all groups was obtained by integrating DSCEP from post-operative days 2 to 35. Statistical comparisons made by one-way ANOVA revealed significant differences among groups ($F_{(3,12)} = 517.54$; $p < 0.00000$) (Fig. 5).

Table 2. — *Statistical comparisons of ocular data in treated and control groups, made by «p x q» ANOVAs.*

	Treatment effect			Time effect			Interaction		
	Freedom degrees	F value	P	Freedom degrees	F value	P	Freedom degrees	F value	P
HSPEV	3,12	9.71	0.0019	4,48	43.52	0.00000	4,48	9.09	0.00000
VSPEV	3,12	30.17	0.00000	4,48	7.34	0.00023	4,48	4.52	0.00017
HSCEP	3,12	94.60	0.00000	4,48	300.87	0.00000	4,48	71.74	0.00000
VSCEP	3,12	118.38	0.00000	4,48	324.86	0.00000	4,48	15.28	0.00000
DSCEP	3,12	176.54	0.00000	4,48	663.92	0.00000	4,48	65.57	0.00000

Fig. 2 – *Compensation of single postural symptoms in treated and control animals.*

The figure illustrates the influence of dopamine active agent treatments on recovery of symmetry in head posture (A), trunk and limb postures (B) and of righting reflexes (C).

Abscissae: time in days from HL; ordinates: degree of severity of vestibular asymmetries.

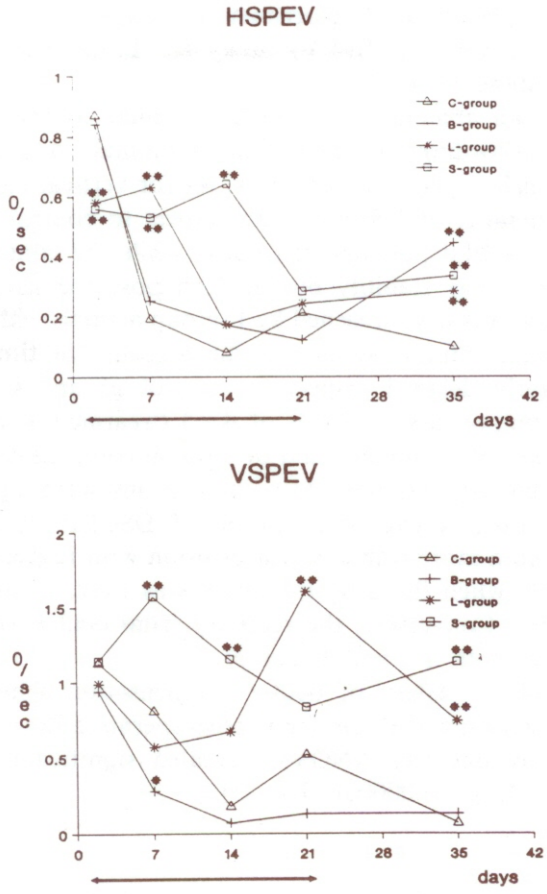

Fig. 3 – *Compensation of ocular asymmetries induced by the right hemilabyrinthectomy in treated and control animals.*

The figure shows the decay of mean Slow Phase Eye Velocity of the horizontal (HSPEV, upper graph) and vertical (VSPEV, lower graph) components of spontaneous drifts.

Abscissae: time in days from hemilabyrinthectomy; ordinates: Slow Phase Eye Velocity (SPEV) calculated in degrees/sec.

DISCUSSION

The present study demonstrates that post-operative treatment with agents active on dopaminergic transmission affects the compensation of the vestibular deficits that follow a unilateral labyrinthectomy.

Treatment with bromocriptine, a D_2 agonist, clearly accelerates vestibular compensation. This effect was observed both on postural and oculomotor recovery, but it was more evident in the compensation of postural deficits. In fact, HL animals treated with bromocriptine regained more promptly and maintained without failures a symmetrical head and body posture, even when drug treatment was

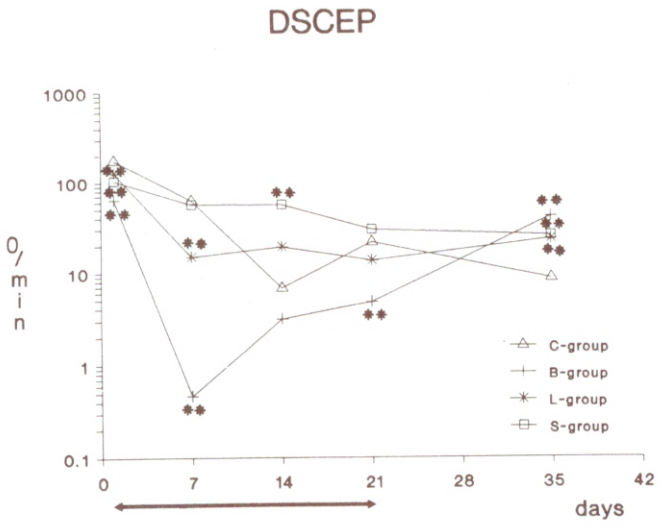

Fig. 4 – *Compensation of ocular asymmetries induced by the right hemilabyrinthectomy in treated and control groups.*

The figure illustrates the decay of Diagonal Slow Cumulative Eye Position (DSCEP) in function of the time. Abscissa: time in days from hemilabyrinthectomy; ordinate: DSCEP, evaluated in degrees/min in a logarithmic scale.

over. Conversely, the suspension of drug administration provoked the renewal of ocular drifts that were significantly reduced during treatment period. The positive effect of bromocriptine on compensation of vestibular deficits is mirrored by the delaying action of the D_2 antagonist sulpiride on such symptoms. Animals treated with sulpiride exhibited a delayed compensation of postural and ocular asymmetries of vestibular origin although the general evolution of symptoms was not altered. Peculiar was the time course of vestibular compensation in the animals treated with lisuride. In this group, it was possible to demonstrate a delay of vestibular recovery so marked that it reached a sort of «freezing» of deficits, some of them beginning a very slow compensation only at the end of drug treatment.

The research on the behavioural functions of the multiple receptors for DA has led to evidence a functional dichotomy of D_1- and D_2-dependent behaviours. Selective D_1 agonists induce contralateral turning, grooming and oral dyskinisia in rats with unilateral nigral lesions. Activation of D_2 receptors has been implicated in DA-mediated locomotion, stereotypy and reward learning processes (6). Drugs administered in this research are all engaging D_2 receptors. The opposite effects of the D_2 agonist bromocriptine and the D_2 antagonist sulpiride on vestibular compensation mimic the opposite effects of dopamine agonists and antagonists in other forms of learning, such as avoidance conditioning and maze discrimination (9, 16). The complex behavioral effect of lisuride may be attributed to a mixed action on various types of receptors, as this ergot derivative is known to interact with adrenergic and serotonergic besides dopaminergic receptors (12, 14).

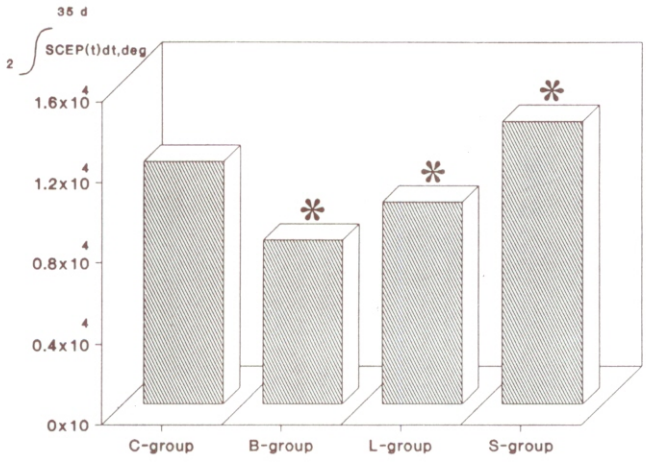

Fig. 5 – *Integration of mean Slow Cumulative Eye Position (SCEP) from post-operative day 2 to 35 in the four experimental groups.*

(* = $p < 0.05$; Tukey's test).

Although the present data do not allow to define the site of action of dopaminergic agents affecting vestibular compensation, one may wonder what is their mode of action in the vestibular recovery. Several data demonstrate a dopaminergic involvement in attentional processes (2) and indicate that drugs acting on DA system, such as amphetamines, modify the time course of vestibular compensation by aspecifically influencing the CNS activity level (20). These results suggest that the effects of D_2 agonists and antagonists used in the present study may be due to a generalized effect on arousal level. Nonetheless, a specific action of DA active agents on the motor behaviour and learning processes involved in the vestibular compensation can be meaningly advanced. In fact, brain catecholamines play a role in regulating neural plasticity in the vestibulo-ocular system (13, 24) just as they appear to do in the visual cortex (10). DA system is significantly involved in posture, locomotor activity and various forms of learning. The integrity of DA transmission is determinant for the normal processing of neural information related to motor function (4, 7, 8). It has repeatedly been observed that pharmacological manipulations decreasing activity in DA systems produce hypoactivity and that, on the other hand, enhanced transmission at the DA synapses increases motor activity or produces stereotypy (4, 14). Alleviation of hypokinetic symptoms by administration of DA agonists has been extensively reported (9). Additionally, several lines of evidence support the hypothesis that central dopaminergic transmission is involved in various learning paradigms, such as delayed alternation tasks, incentive motivational learning, avoidance response (4). Direct pharmacological manipulation of the DA activity by systemic administration of both agonist and antagonist drugs provides further evidence of a role for DA in acquisition, storage and retrieval of information (16). Finally, electrophysiological data indicate that DA neurons could modulate sensorimotor integration involved in learning process-

es, by mediating changes in synaptic effectiveness that influence and regulate system responses, selecting thus inputs with reinforcing properties (29). All these functions of DA system are of particular interest in our model. Vestibular compensation is a learning process based on motor commands continuously readjusting in connection with the new state of the system. Information about past performances is used as a reference framework to make the next motor acts better than the last ones. Thus, it is a goal-directed learning process, result of a continuous error correction and action planning (28), in which agents known to influence motor control and learning processes, such as DA active agents, can play a significant role.

SUMMARY

The aim of the present work was to examine the effects of postoperative treatments with agents active on dopaminergic system on vestibular recovery from the postural and ocular symptoms which follow a unilateral labyrinthectomy. Hemilabyrinthectomized guinea pigs were given a daily i.p. injection of bromocriptine (1 mg/kg) or sulpiride (10 mg/kg) or lisuride (0.1 mg/kg) or saline from post-operative days 1 to 21. Treatment with bromocriptine, a D_2 agonist, accelerates compensation of postural and ocular symptoms. Conversely, treatment with sulpiride, a D_2 antagonist, slows down the reachievement of symmetrical posture and stable ocular motility. Finally, the lisuride treatment, a drug active on D_2 but also on other monoaminergic receptors, delays vestibular recovery so markedly to reach a «freezing» of vestibular deficits during drug treatment. These findings indicate that the already demonstrated role of dopamine in motor activity and learning can be extended to the learning processes required to recover from vestibular asymmetries.

Acknowledgements. — The study of vestibular system is the *fil rouge* that ideally links the first studies of the school Prof. E. Manni comes from, with the researches carried out by him and his collaborators in Sassari and Rome, and finally with the studies that, with different facets, many of his numerous collaborators continue dealing with. Thus, we are very glad to dedicate to Prof. Manni this research on a subject so dear to him. We gratefully acknowledge the technical assistance of Mrs Barbara Zannoni. This research was supported by CNR and MPI grants.

REFERENCES

1. Abeln, V., Bienhold, H. and Flohr, H. Influence of cholinomimetics and cholinolytics on vestibular compensation. *Brain Res.*, **222**: 458-462, 1981.
2. Archer, T. and Sagvolden, T. Basic mechanisms of drug action: catecholaminergic

issues. Pp. 191-197. In T. SAGVOLDEN and T. ARCHER (Eds.), *Attention Deficit Disorder*. Hillsdale, N.J., Lawrence Erlbaum Ass. Publ., 1989.
3. BARMACK, N. H. A comparison of horizontal and vertical vestibulo-ocular reflexes of the rabbit. *J. Physiol., Lond.*, **314**: 547-564, 1981.
4. BENINGER, R. J. The role of dopamine in locomotor activity and learning. *Brain Res. Rev.*, **6**: 173-196, 1983.
5. CALZÀ, L., GIARDINO, L., ZANNI, M., GALETTI, R., PARCHI, P. and GALETTI, G. Involvement of cholinergic and GABA-ergic systems in vestibular compensation. Pp. 189-199. In M. LACOUR, M. TOUPET, P. DENISE and Y. CHRISTEN (Eds.), *Vestibular Compensation: Facts, Theories and Clinical Perspectives*. Paris, Elsevier, 1989.
6. CHIODO, L. A. Dopamine-containing neurons in the mammalian central nervous system: electrophysiology and pharmacology. *Neurosci. & Biobehav. Rev.*, **12**: 49-91, 1988.
7. FLETCHER, G. H. and STARR, M. S. Role of the substantia nigra in the expression of dopamine D_1 receptor-mediated and D_2 receptor-mediated behaviours. *Neurosci.*, **23**: 1001-1010, 1987.
8. FREED, C. R. and YAMAMOTO, B. K. Regional brain dopamine metabolism: a marker for the speed, direction and posture of moving animals. *Science*, **229**: 62-65, 1985.
9. GERSHANIK, O., HEIKKILA, R. E. and DUVOISIN, R. C. Behavioral correlations of dopamine receptor activation. *Neurology*, **33**: 1489-1492, 1983.
10. KASAMATSU, T. and PETTIGREW, J. D. Preservation of binocularity after monocular deprivation in the striate cortex of kittens treated with 6-hydroxydopamine. *J. Comp. Neurol.*, **185**: 139-162, 1979.
11. KASIK, P., COCHRAN, S. L., DIERINGER, N. and PRECHT, W. Evidence for an alteration in brainstem cholinergic pathways following unilateral labyrinthectomy in the frog. *Brain Res.*, **363**: 188-191, 1986.
12. KEHR, W. Effect of lisuride and other ergot derivatives on monoaminergic mechanisms in rat brain. *Eur. J. Pharmacol.*, **41**: 261-273, 1987.
13. KELLER, E. L. and SMITH, M. J. Suppressed visual adaptation of the vestibulocular reflex in catecholamine-depleted cats. *Brain Res.*, **258**: 323-327, 1983.
14. LAHOSTE, G. J. and MARSHALL, J. F. Nigral D_1 and striatal D_2 receptors mediate the behavioral effects of dopamine agonists. *Behav. Brain Res.*, **38**: 233-242, 1990.
15. LICATA, F., LI VOLSI, G., MAUGERI, G. and SANTANGELO, F. Effects of 5-hydroxytryptamine on the firing rates of neurons of the lateral vestibular nucleus in the rat. *Exp. Brain Res.*, **79**: 293-298, 1990.
16. PACKARD, M. G. and WHITE, N. M. Memory facilitation produced by dopamine agonists: role of receptor subtype and mnemonic requirements. *Pharmacol. Biochem. & Behav.*, **33**: 511-518, 1989.
17. PEPPARD, S. B. Effect of drug therapy on compensation from vestibular injury. *Laryngoscope*, **96**: 878-898, 1986.
18. PETROSINI, L. Behavioural recovery from unilateral vestibular lesion is facilitated by GM1 ganglioside treatment. *Behav. Brain Res.*, **23**: 117-126, 1987.
19. PETROSINI, L. and GREMOLI, T. Spontaneous eye motility following a unilateral vestibular lesion. *Brain Res.*, **418**: 398-402, 1987.
20. SMITH, P. F. and CURTHOYS, I. S. Mechanisms of recovery following unilateral labyrinthectomy: a review. *Brain Res. Rev.*, **14**: 155-180, 1989.
21. SMITH, P. F. and DARLINGTON, C. L. The NMDA antagonists MK801 and CPP disrupt compensation for unilateral labyrinthectomy in the guinea pig. *Neurosci. Lett.*, **94**: 309-313, 1988.
22. SMITH, P. F. and DARLINGTON, C. L. Neurochemical mechanisms of recovery from peripheral vestibular lesions (vestibular compensation). *Brain Res. Rev.*, **16**: 117-133, 1991.
23. STEINBUSCH, H. W. M. Distribution of histaminergic neurons and fibers in rat brain. *Acta Otolaryngol., Stockh.*, **479**: 12-23, 1991.

24. VAN NEERVEN, S., POMPEIANO, O., COLLEWIJN, H. and VAN DER STEEN, J. Injections of β-noradrenergic substances in the flocculus of rabbits affect adaptation of the VOR gain. *Exp. Brain Res.*, **79**: 249-260, 1990.
25. DE WAELE, C., VIBERT, N., BAUDRIMONT, M. and VIDAL, P. P. NMDA receptors contribute to the resting discharge of vestibular neurons in the normal and hemilabyrinthectomized guinea pig. *Exp. Brain Res.*, **81**: 125-133, 1990.
26. WALBERG, F., OTTERSEN, O. P. and RINVIK, E. GABA, glycine, aspartate, glutamate and taurine in the vestibular nuclei: an immunocytochemical investigation in the cat. *Exp. Brain Res.*, **79**: 547-563, 1990.
27. WINER, B. J. *Statistical Principles in Experimental Design*. New York, McGraw-Hill, 1962.
28. XERRI, C. and ZENNOU, Y. Sensory, functional and behavioral substitution processes in vestibular compensation. Pp. 35-58. In M. LACOUR, M. TOUPET, P. DENISE and Y. CHRISTEN (Eds.), *Vestibular Compensation: Facts, Theories and Clinical Perspectives*. Paris, Elsevier, 1989.
29. YIM, C. Y. and MOGENSON, G. J. Response of nucleus accumbens neurons to amygdala stimulation and its modification by dopamine *Brain Res.*, **239**: 401-415, 1982.