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STRUCTURAL-FUNCTIONAL RELATIONSHIPS IN CEREBELLAR AND VESTIBULAR SYSTEMS

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INTRODUCTION

An effective strategy often adopted in the investigation of brain mechanisms is to look for structural-functional relationships in brain tissues. Any specific brain function should be embodied in a distinct brain structure, and a specific brain structure should reflect a distinct brain function. The numerous articles and monographs written by the late Professor Alf Brodal and his associates were full of valuable suggestions in this respect. In particular, the monograph by Brodal, Pompeiano and Walberg (4) was our reference book through the 1960's. I shall raise here some examples of suggestions from his writings, for which I can find fruitful outcome in recent findings and formulation of new concepts about cerebellar and vestibular systems.

Purkinje cell inhibition on Deiters neurons.

Anatomical data on the long cerebellofugal projection by Purkinje cells to vestibular nuclei (4) provided excellent ground for electrophysiological studies on cerebellar and vestibular systems. These data guided our earlier finding that electrical stimulation of the cerebellar cortex produced monosynaptic inhibition in Deiters neurons (17), which lead to an important conclusion that Purkinje cells supply inhibitory synapses onto Deiters neurons. The unique spatial pattern of Purkinje cell projection from the lateral vermis to ipsilateral dorsal Deiters neurons (29) was a key for identifying Purkinje cells as inhibitory, because monosynaptic inhibition was induced specifically by stimulation of the lateral vermis and predominated in ipsilateral dorsal Deiters neurons (1, 18).

It appeared difficult, though, to convince Prof. Alf Brodal with a generalization that all Purkinje cells are specialized as inhibitory neurons (3). I proposed this generalization by showing that cerebellar cortical stimulation regularly induced monosynaptic inhibition in all subdivisions of cerebellar nuclei (19), but of course it was not possible to test all Purkinje cells in this manner.

Neverthless, recent immunohistochemical data that virtually all Purkinje cells contain GAD which synthesizes inhibitory neurotransmitter GABA (24) strongly support the postulation of the exclusive inhibitory action of Purkinje cells.

Immunohistochemical data also revealed chemical heterogeneity of Purkinje cells; some, but not all, Purkinje cells contain motilin (7, 23) and/or taurine (8, 28) in addition to GAD. Nevertheless, both motilin and taurine exhibit potent inhibitory action when applied iontophoretically onto Deiters neurons (9), and therefore there will be no conflict with the postulation that all Purkinje cells are inhibitory, even when not only GABA but also motilin or taurine acts as a neurotransmitter of Purkinje cells. The implications of this chemical heterogeneity of Purkinje cells are not yet well understood.

Synaptic organization in Deiters neurons.

While Purkinje cells of the lateral vermis (B zone) project to dorsal Deiters neurons directly, those of the medial vermis (A zone) project to fastigial nuclear neurons which in turn project to Deiters neurons, not only dorsal but also ventral (4). The organization of synaptic input to Deiters neurons is further complicated by the fact that excitatory synapses supplied from primary vestibular afferents impinge onto ventral, but not dorsal Deiters neurons, though there is an overlap between Purkinje cell inhibition and vestibular excitation in an intermediate zone of the nucleus of Deiters (1, 30). Another complication is that a spinal ascending tract also provides an excitatory input to Deiters neurons (1, 4). Deiters neurons thus offer an interesting test case for our effort to elucidate the complex structural-functional relationships of the brain. I tried to do so based on the concept of a corticonuclear microcomplex of the cerebellum (15).

A corticonuclear microcomplex consists of a cerebellar cortical microzone and an associated small group of nuclear neurons (in a vestibular or cerebellar nucleus) (Fig. 1). Afferents conveying a specific input to nuclear cells provide a major pathway for signal transmission, while a cortical microzone, which relays the same specific input through mossy fiber circuits, forms a sidepath to the major nuclear pathway. A small group of inferior olivary neurons supplies climbing fiber afferents to a corticonuclear microcomplex. Climbing fiber signals represent errors in the overall performance of a neural control system involving the corticonuclear microcomplex, and act to modify transfer characteristics of mossy fiber signals across the microzone by invoking synaptic plasticity (long-term depression) in Purkinje cells. Thus, a corticonuclear microcomplex constitutes a modifiable sidepath element which parallels a nuclear pathway subserving a bodily function.

To constitute such a corticonuclear microcomplex, a nuclear group must receive Purkinje cell input from a microzone, as defined by Oscarsson (25), and an excitatory input from mossy fiber afferents which pass onto that microzone at the same time. It is noted that some Deiters neurons receive primary vestibular input and also Purkinje cell input from the vermis which is, however, not impinged upon by primary vestibular afferents except for the lingula (6, 10). Such connections do not properly represent a cortico-nuclear microcomplex, because Purkinje cell projection is not coupled with the primary vestibular afferent. Instead, the

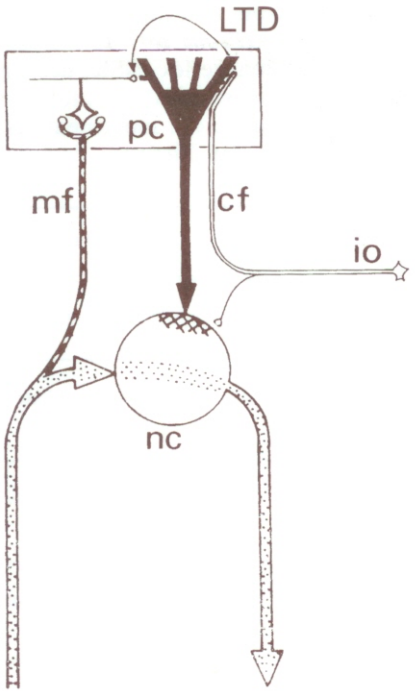

Fig. 1. – *Structure of a corticonuclear microcomplex: Form A.*

Applicable to the flocculo-VOR system. mf, mossy fiber. cf, climbing fiber. pc, Purkinje cell. nc, nuclear cell. io, inferior olive. LTD, long-term depression.

vermal Purkinje cell projection to Deiters neurons has been shown to be coupled with a spinal ascending tract which supplies collaterals to Deiters neurons and which passes onto the vermis as mossy fibers (1). In other words, the vermis-Deiters microcomplex is attached to a spino-vestibulo-spinal pathway (Table 1D), but not to a primary vestibular-vestibulospinal pathway (Table 1A).

The complicated anatomical and physiological data are thus interpreted as indicating that in addition to the above mentioned situation (Table 1A), at least four more subsystems, each subserving a specific bodily function, are superimposed in the nucleus of Deiters (Table 1B-E). It is noted that one and the same Deiters neuron can be involved in more than one of these subsystems.

Flocculo-vestibular system.

Anatomical data that the flocculus Purkinje cells project to vestibular nuclei and that primary vestibular afferents pass into the flocculus (2, 6) motivated our earlier efforts to identify function of these connections. It was found that flocculus

Table 1. — *Cerebellovestibular subsystems with different corticonuclear microcomplex compositions and functional implications. (From ref. 15).*
FN, fastigial nucleus. VSR, vestibulospinal reflex. NSR, neck-spinal reflex. VCR, vestibulocolic reflex. TLR, tonic labyrinthine relex. SVSL, spinovestibulo-spinal loop riding over spinal segmental reflexes. OKR, optokinetic eye movement response. vest., vestibular. asc. tr., ascending tract. LRN, lateral reticular nucleus.

	MF input	microzone	nuclear neurons	function
A	1ry vest.	none	ventral Deiters	VCR
B	1ry vest. & neck	lingula	intermediate Deiters	VSR NSR
C	2ry vest.	lateral vermis	dorsal Deiters	TLR
D	spinal asc. tr.	lateral vermis	dorsal Deiters	SVSL
E	LRN	medial vermis	FN projecting to Deiters	locomotion
F	1ry vest.	flocculus	medial-superior vest. nuclei	VOR OKR

Purkinje cells specifically supply inhibitory synapses to those vestibular nuclear neurons which are driven by primary vestibular afferent signals and which in turn drive oculomotor neurons (20). Thus, the flocculus constitutes with vestibular nuclear neurons a corticonuclear microcomplex subserving the vestibulo-ocular reflex (VOR) (Fig. 2A and Table 1F). The flocculus hypothesis of the VOR control postulates that the flocculus is the center of adaptive control for the VOR (13, 14).

The subsystem of the VOR (Table 1F) provides a marked contrast with the subsystem of the VCR (vestibulocolic reflex, Table 1A) in that a corticonuclear microcomplex is attached to the VOR but not to VCR, in spite of the fact that both VOR and VCR have a rather similar structure in their reflex arcs. From the viewpoint of control theories (14), the VOR is a feed-forward control system lacking feedback from output (eye velocity or position) to input (head position or velocity), while the VCR is a typical closed-loop control system equipped with efficient feedback from output to input, both representing head velocity or posi-

tion. The VCR secures the stability of the head due to its closed-loop control performance, but the VOR cannot secure by itself the stability of retinal images due to lack of feedback.

The role of the flocculus can thus be defined clearly in the following manner (16). While the VOR is a feedforward system which cannot perform precision work by itself because of the lack of feedback, the flocculus provides a modifiable element in the system effected by retinal error signals conveyed through climbing fibers. The overall performance of the VOR system would be continuously modified toward minimization of retinal errors. To eliminate retinal errors, the output of the VOR (eye velocity or position) should be equal to the input (head velocity or position), with the sign reversed. Thence, when fully adapted, the dynamics of the corticonuclear microcomplex in this system, including the vestibular organs, vestibular nuclei and the flocculus, should be inversely equal (i.e., 1/G) to the dynamics (G) of the oculomotor part of the system composed of oculomotor neurons, extraocular muscles and the eyeball (Fig. 2B). The role of the corticonuclear

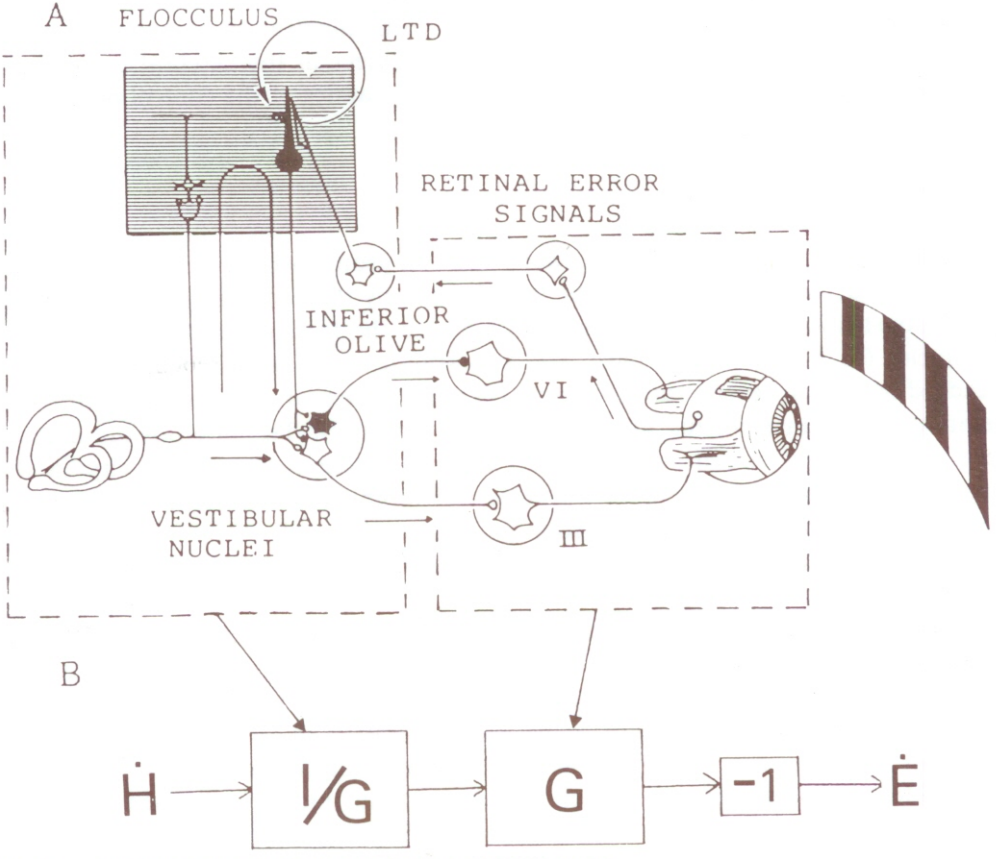

Fig. 2. – *Control system structure of the flocculo-VOR system.*

A, major pathwas for the VOR. LTD, lon-term depression. III and IV, oculomotor and abducens cranial nuclei. B, block diagram showing the control system structure implied in A. Ḣ. head velocity. Ė, eye velocity.

microcomplex part is to provide exact inverse dynamics of the oculomotor part with the aid of the synaptic plasticity in flocculus Purkinje cells.

This control scheme can be expanded to a general theory of neural control which is applicable to the cerebellar control of voluntary movements (16). While the motor cortex and associated cerebral cortices perform voluntary movement control by referring to sensory feedback, a cerebellar corticonuclear microcomplex operates as a feedforward controller in parallel with the cerebral cortices but without sensory feedback. During exercises performed by the cerebral cortices, the cerebellar controller will be progressively adjusted to achieve the exact inverse dynamics of the control object, which may be an arm or a leg. Once adjusted in this way, the corticonuclear microcomplex alone would perform the voluntary control without affecting the cerebral cortex. This would constitute the mechanism of motor learning, which has in fact been successfully computer-simulated for the manipulation of a robot arm (21).

The same scheme would apply to cerebellar control of mental activity recently proposed (11, 22, 26), if not only the feedback controller but also the control object are placed in the cerebral cortex. A corticonuclear microcomplex would act as a feedforward controller for the control object in the cerebral cortex after its dynamics are adjusted to simulate the inverse dynamics of the control object (16).

Reverberation circuits.

Mutual excitatory connections between two cell groups would cause a reverberating impulse activity circulating in the ring formed by the two cell groups. Anatomical demonstration of mutual connections between the fastigial nucleus and vestibular nuclei (4) has been the basis for a postulate that the cerebellar nuclei are attached with such reverberation circuits (12) and an actual demonstration of reverberation in the interpositus nucleus by Tsukahara (27). The interpositus neurons form a reverating circuit with a group of brain stem neurons. Activity in this circuit is normally depressed by Purkinje cell inhibition of interpositus neurons, but it is put into reverberation as soon as the Purkinje cell inhibition is removed, and builds a large sustained depolarization in red nucleus neurons which receive excitatory inputs from interpositus neurons.

There is no evidence of such reverberation circuit attached to the VOR arc; presumably, tonic discharges from vestibular organs provide sufficient background activity for the floccular corticonuclear microcomplex. However, in a case where such background activity may not occur, a reverberation circuit would be indispensable. Furthermore, it is possible that with a reverberation circuit attached, a corticonuclear microcomplex may function even without nuclear collaterals of mossy fibers (Fig. 3). In this case, a specific mossy fiber input is transferred through a microzone and acts through Purkinje cell axons upon the background activity provided by the reverberation circuit.

Sparseness of nuclear collaterals has been pointed out in mossy fibers arising

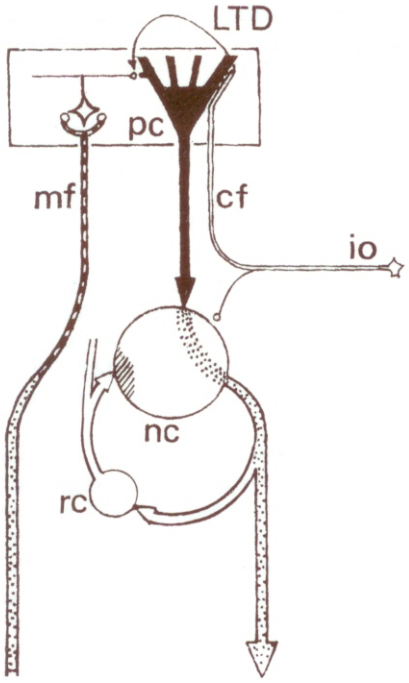

Fig. 3. – *Structure of a corticonuclear microcomplex: Form B.*

Applicable to the hemispheric part of the cerebellum. rc, reverberation circuit neuron in the brain stem.

from pontine nuclei, which supply few collaterals to the lateral cerebellar nucleus when passing to the cerebellar hemispheral cortex (5). By contrast, mossy fibers arising from the nucleus reticularis tegmenti pontis (NRTP) give rise to collaterals to the lateral cerebellar nucleus. It is possible that pontine nuclei and NRTP share their roles in the manner illustrated in Fig. 3: pontine nuclei as a source of specific input and NRTP as a reverberation circuit. It is an interesting future task to compare the functional modes of these two major sources of mossy fibers to the hemispheral part of the cerebellum, and to clarify the essential difference between the two proposed principal structures of corticonuclear microcomplexes (Figs. 1 and 3).

CONCLUSIONS

The late Professor Alf Brodal's rigorous, highly systematic investigation and accurate description of anatomical features have been a solid basis for recent advancement in physiology of vestibular and cerebellar systems. This situation seems to testify the validity of the strategy to approach brain mechanisms through

analyses of structural-functional relationships of brain tissues and suggests its productiveness in future neuroscience.

REFERENCES

1. AKAIKE, T., FANARDJIAN, V.V., ITO, M. and NAKAJIMA, H. Cerebellar control of the vestibulospinal tract cells in rabbit. *Exp. Brain Res.*, **18**: 446-463, 1973.
2. ANGAUT, P. and BRODAL, A. The projection of the vestibulocerebellum onto the vestibular nuclei in the cats. *Arch. ital. Biol.*, **105**: 441-479, 1967.
3. BRODAL, A. *Neurological Anatomy, in Relation to Clinical Medicine*. 3rd edition, Oxford Univ. Press. p. 305, 1984.
4. BRODAL, A. POMPEIANO, O. and WALBERG, F. *The vestibular Nuclei and their Connexions, Anatomy and Functional correlations*. Springfield, III/C.C. Thomas, 1962.
5. BRODAL, P., DIETRICHS, E. and WALBERG, F. Do pontocerebellar mossy fibres give off collaterals to the cerebellar nuclei? An experimental study in the cat with implantation of crystalline HRP-WGA. *Neurosci. Res.*, **4**: 12-24, 1986.
6. BRODAL, A. and HØIVIK, B. Site and termination of primary vestibulo-cerebellar fibres in the cat. An experimental study with silver impregnation methods. *Arch. ital. Biol.*, **102**: 1-21, 1964.
7. CHAN-PALAY, V., NILAVER, G., PALAY, S.L., BEINFELD, M.C., ZIMMERMAN, E.A., WU, J.Y. and D'DONOHUE, T.L. Chemical hetero-geneity in cerebellar Purkinje cells: Existence and coexistence of glutamic acid decarboxylase-like and motilin-like immunoreactivities. *Proc. Roy. Natl. Acad. Sci. USA*, **78**: 7787-7791, 1981.
8. CHAN-PALAY, V., PALAY, S.L. and WU, J.-Y. Sagittal cerebellar microbands of taurine neurones: immunocyto-chemical demonstration by using antibodies against the taurine-synthesizing enzyme cystein sulfinic acid decarboxylase. *Proc. Natl. Acad. Sci. USA*, **79**: 4221-4225, 1982.
9. CHAN-PALAY, V., ITO, M., TONGROACH, P., SAKURAI, M. and S.L. PALAY. Inhibitory effects of motilin, somatostatin, (leu)enkephalin, (met)enkephalin, and taurine on neurons of the lateral vestibular nucleus: interaction with γ-amino butyric acid. *Proc. Natl. Acad. Sci. USA*, **79**: 3355-3359, 1982.
10. HIRAI, N. Input-output relations of lobules I and II of the cerebellar anterior lobe vermis in connexion with neck and vestibulospinal reflexes in the cat. *Neurosci. Res.*, **4**: 167-184, 1987.
11. INGVAR, P. In: *Principles of design and Operation of the Brain*, ed. Eccles, J.C., Springer-Verlag, Berlin, 1990, in press.
12. ITO, M. Neurons of cerebellar nuclei. In: *Interneuron*, ed. Brazier, A.B. UCLA Forum 309-327, 1969.
13. ITO, M. Neural design of the cerebellar motor control system. *Brain Res.*, **40**, 81-84, 1972.
14. ITO, M. The control mechanisms of cerebellar motor system. In: *The Neurosciences, Third Program*, eds. Schmitt, F.O. and WORDEN, F.G. 293-303, MIT Press, 1974.
15. ITO, M. *The Cerebellum and Neural Control*, Raven Press, New York, 1984.
16. ITO, M. Neural control as a major aspect of high-order brain function. In: *Principles of Design and Operation of the Brain*, ed. ECCLES, J.C. Springer-Verlag, Berlin, 1990 in press.
17. ITO, M. and YOSHIDA, M. The origin of cerebellar-induced inhibition of Deiters neurones. I. Monosynaptic initiation of the inhibitory postsynaptic potentials. *Exp. Brain Res.*, **2**: 330-349, 1966.

18. Ito, M., Kawai, N. and Udo, M. The origin of cerebellar-induced inhibition of Deiters neurones. III. Localization of the inhibitory zone. *Exp. Brain Res.*, **4**: 310-320, 1968.
19. Ito, M., Yoshida, M., Obata, K., Kawai, N. and Udo, M. Inhibitory control of intracerebellar nuclei by the Purkinje cell axons. *Exp. Brain Res.*, **10**: 64-80, 1970.
20. Ito, M., Highstein, S.M. and Fukuda, J. Cerebellar inhibition of the vestibulo-ocular reflex in rabbit and cat and its blockage by picrotoxin. *Brain Res.*, **17**: 524-526, 1970.
21. Kawato, M., Furukawa, K. and Suzuki, R. A hierarchical neural network model for control and learning of voluntary movement. *Biol. Cybern.*, **57**: 169-185, 1987.
22. Leiner, H.C., Leiner, A.L. and Dow, R.S. Does the cerebellum contribute to mental skill? *Behav. Neurosci.*, **100:** 443-453, 1986.
23. Nilaver, G., Defendini, R., Zimmerman, E.A., Beinfeld, M.C. and O'Donohue, T.L. Motilin in the Purkinje cell of the cerebellum. *Nature*, **295**: 597-598, 1982.
24. Oertel, W.H., Schmechel, D.E., Mugnaini, E., Tappaz, M.L. and Kopin, I.J. Immunocytochemical localization of glutamate decarboxylase in rat cerebellum with a new antiserum. *Neuroscience*, **6**: 2715-2735, 1981.
25. Oscarsson, O. Functional units of the cerebellum-sagittal zones and microzones. *Trends Neurosci.*, **2**: 143-145, 1979.
26. Petersen, S., Fox, P.T., Posner, M.I., Mintum, M. and Raichle, M.E. Positron emission tomographic studies of the processing of single words. *J. Cog. Neurosci.*, **1**: 153-170, 1989.
27. Tsukahara, N. The properties of the cerebellopontine reverberating circuit. *Brain Res.*, **40**: 67-71, 1972.
28. Yoshida, M., Karasawa, N., Ito, M., Sakai, M. and Nagatsu. I. Demonstration of taurine-like immunoreactive structure in the rat brain. *Neurosci. Res.*, **3**: 356-363, 1986.
29. Walberg, F. and Jansen, J. Cerebellar corticonuclear projections studied experimentally with silver impregnation method. *J. Hirnforschung*, **6**: 338-354, 1964.
30. Walberg, F. and Mugnani, Distinction of degenerating fibers and boutons of cerebellar and peripheral origin in the Deiters' nucleus of the same animal. *Brain Res.*, **14**: 67-75, 1969.