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Comparative Aspects of Cerebellar Organization

From Mormyrids to Mammals

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ABSTRACT

Recent progress in the comparative analysis of the vertebrate cerebellar organization shows that the cerebella of different tetrapods have a basically similar intrinsic organization, whereas the cerebellum of fishes displays a number of fundamental differences in this respect. Clear examples of teleostean cerebellar specializations are present in the gigantocerebellum of mormyrids, including a valvula cerebelli, the absence of a parasagittal zonal organization, the presence of eurydendroid projection neurons instead of deep cerebellar nuclei, a precerebellar nucleus lateralis valvulae, olivocerebellar fibers that do not climb into the molecular layer, uni- and bilateral locations of granule cells, parallel fibers without a T-shaped bifurcation and with a coextensive distribution in the transverse plane, and different Purkinje cell arrangements including a dendritic palisade pattern. A theoretical exploration of the possible significance of these configurations suggests that they all might be involved in a single main cerebellar function, i.e. coincidence detection of parallel fiber activity by Purkinje cells.

KEYWORDS: parallel fibers – Purkinje cells – granule cells – molecular layer – coincidence detection

INTRODUCTION

The cerebellum is one of the most investigated regions of the vertebrate brain, and particularly the mammalian cerebellum has been the focus of many anatomical, physiological, pharmacological and behavioral studies (see Eccles, 1967; Ito, 1984). However, since the publication of Nieuwenhuys' Comparative Anatomy of the Cerebellum (1967) (see also Larsell, 1967), significant progress has been made as well in the understanding of the organization of non-mammalian cerebella. It is the purpose of the present contribution to survey recent comparative studies on the cerebellar organization, in particular those executed in the department of Anatomy and Embryology in Nijmegen under the direction of Nieuwenhuys, with emphasis on mormyrid teleosts. The possible functional significance of the variabilities and constraints encountered during this survey will be explored, and it will be concluded that these strongly suggest that mammalian as well as non-mammalian Purkinje cells are all involved in coincidence detection of parallel fiber activity (Meek, 1992).

THE MAMMALIAN CEREBELLUM

As summarized in several reviews (e.g., Eccles, 1967; Ito, 1989; Nieuwenhuys, 1985; Nieuwenhuys et al., 1985) the cerebellar cortex consists of three layers: an outer molecular layer with few neuronal cell bodies; a monolayer of large Purkinje cells; and a deep granular layer with numerous small granule cells. The latter receive excitatory synaptic input from mossy fibers, which have a variety of extracerebellar origins, and send bifurcating axons, termed parallel fibers, to the molecular layer, where they make excitatory synaptic contacts with spines on the dendrites of Purkinje cells. Whereas the parallel fibers are oriented in the transverse direction, the dendritic trees of Purkinje cells are oriented in the sagittal plane, which results in the well-known orthogonal organization of the molecular layer. Apart from parallel fiber input, Purkinje cells receive input from climbing fibers, which originate from the inferior olive and 'climb' along the Purkinje cell dendrites in the molecular layer. Whereas the granule cell input on Purkinje cells is highly convergent, each Purkinje cell is only contacted by one climbing fiber. Purkinje cells project to central cerebellar nuclei, whose activity is inhibited by the GABAergic Purkinje cells. Cerebellar output originates from these central cerebellar nuclei, and is distributed over a variety of brain regions, predominantly involved in motor control.

In addition to the excitatory mossy fiber- parallel fiber- Purkinje cell- and climbing fiber-Purkinje cell pathways just described, three inhibitory feedback loops are present in the mammalian cerebellar cortex, established by stellate cells in the molecular layer, basket cells in the Purkinje cell layer and Golgi cells in the granular layer. These elements receive similar excitatory input from parallel fibers, but their axonal targets are different: stellate cells make inhibitory synaptic contacts on the smooth surface of Purkinje cell dendrites; basket cells make basket-like inhibitory synaptic contacts with the cell bodies of Purkinje cells; and Golgi cells make inhibitory synaptic contacts with granule cells. Inhibitory effects on Purkinje cell activity may also be exerted by noradrenergic and serotonergic cerebellar inputs (see Nieuwenhuys, 1985).

An interesting aspect of the mammalian cerebellar organization is its parasagittal zonal organization. A number of studies have convincingly demonstrated the existence of parasagittal zones of Purkinje cells with different afferent and efferent connections (e.g., Voogd & Bigaré, 1980) as well as different (immuno)histochemical properties (Hawkes & Gravel, 1991). In rats, these zones are about 2 mm wide in the vermis (midline) region, and up to about 5 mm wide in the hemispheres. Since the parallel fiber length in rat has been estimated to be on average 5 mm (Harvey & Napper, 1991), this suggests that parallel fibers in the vermis might traverse two or three zones, whereas those in the hemispheres might be restricted to a single zone.

NON-MAMMALIAN CEREBELLA

A first comparison of cerebella of different vertebrate classes shows dramatic differences in the relative size of this brain region (Fig. 1). Being quite small in agnathans, it is well developed in most fishes but again rather small in amphibians and reptiles. A foliated cerebellum is only observed in birds and mammals, where cerebellar size is substantial, although in mammals surpassed by the huge outgrowth of the neocortex.

Apart from their different size and foliation, other aspects of the cerebellar organization of amphibians, reptiles and birds are basically similar to those of mammals, as already described by Nieuwenhuys (1967) and Larsell (1967). In all tetrapods, the cerebellum consists of three layers (a molecular, Purkinje cell- and granular layer), and contains a similar mossy fiber – parallel fiber – Purkinje cell – central nuclei – circuitry, climbing fiber input and inhibitory feedback loops as described above for mammals. This has led to the concept of a basic cerebellar circuitry (Llinás, 1969), which means that all the elements just enumerated belong to the basic cerebellar outfit and are basically similar in the cerebella of tetrapods.

More recent investigations have corroborated the concept of a basic cerebellar circuitry, and extended it to the extracerebellar circuitry. Bangma & ten Donkelaar (e.g., 1982;

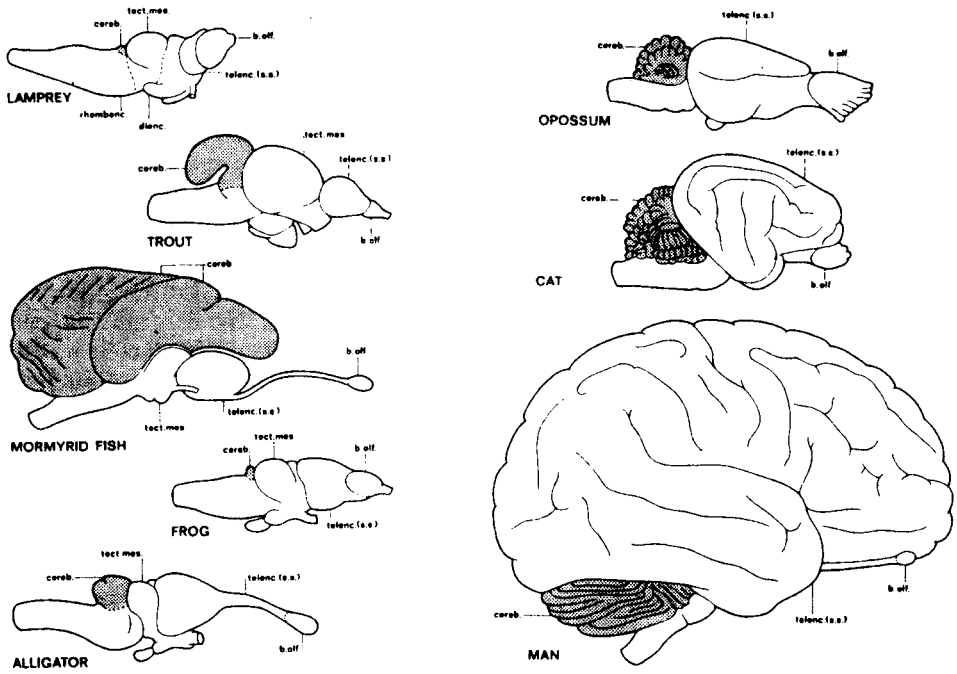

Fig. 1. Comparison of the gross features of the brains of a variety of vertebrates, with emphasis on the relative size of the cerebellum. This figure has been designed by Nieuwenhuys, about 20 years ago, for a lecture on the contributions of L. Edinger, J.B. Johnston and C.J. Herrick to comparative neuroanatomy. A magnified color version has adorned for about 20 years the stair case of the third floor of the Department of Anatomy and Embryology in Nijmegen. In the color version, the cerebellum is blue, the telencephalon yellow and the olfactory bulb pink.

Bangma et al., 1983; Bangma, 1983) have shown that the reptilian cerebellum has basically similar afferent and corticonuclear connections as the mammalian one, while van der Linden and ten Donkelaar showed a similar tendency for the amphibian cerebellum (e.g., Van der Linden et al., 1988; Van der Linden & ten Donkelaar, 1990; Van der Linden, 1990). In addition, birds (e.g., Feirabend & Voogd, 1986) and reptiles (Bangma, 1983) have a similar parasagittal cerebellar organization as mammals. So, apart from their variability in size, comparison of the cerebellum of tetrapods reveals predominantly basic similarities in cerebellar organization. In contrast, comparison of teleosts and other fishes with mammals shows a number of basic differences and a large variability, as will be surveyed in the next section.

TELEOSTEAN CEREBELLA

Comparison of the teleostean and mammalian cerebellum shows already at the macroscopic level two main differences (Figs. 1, 2). First, the cerebellum of teleosts is not a foliated but a tubular structure, and secondly it has a rostral protrusion, termed valvula cerebelli,

fish

a structure only present in actinopterygians and not in any other vertebrate (Nieuwenhuys, 1967; Larsell, 1967). Microscopical analysis has shown that basic differences also exist with respect to the laminar organization and the extrinsic and intrinsic cerebellar circuitry.

The teleostean cerebellum may be subdivided into three main subdivisions: the rostral valvula cerebelli, the centrally located corpus cerebelli, and the caudal lobe (Fig. 2). The valvula is a rostral protrusion in the midbrain ventricle under the midbrain tectum, with a variable size and shape (Fig. 2), and with in some species not only a medial, but also a lateral part (Finger, 1983). It receives a specific set of afferent connections, different from those of the corpus (e.g., Wullimann & Northcutt, 1988, 1989). It was already indicated by Nieuwenhuys (1967) as a tertiary lateral line center, and receives in some teleosts even direct lateral line input (Wullimann et al., 1991). The corpus is the only cerebellar part visible at the external surface of the brain of most teleosts. It is basically a tubular structure directed either rostrally or caudally in different teleosts, with all kinds of intermediate positions (Fig. 2). At last, the caudal lobe is a caudal cerebellar region, possibly homologous to the tetrapodian vestibulocerebellum, with strong relations with the central lateral line sensory region.

With respect to the extrinsic connectivity of the teleostean cerebellum, two main differences with most tetrapods may be noticed. First, cerebellar output does not arise from central cerebellar nuclei, since these are absent in teleosts. Instead, cerebellar output arises from so-called eurydendroid neurons, a name introduced by Nieuwenhuys et al. (1974). These were first described in the cerebellum of mormyrids (Nieuwenhuys & Nicholson, 1969b; Nieuwenhuys et al., 1974; see also Meek et al., 1986a,b), and later studies corroborated their existence and extracerebellar projections in the trout (e.g., Pouwels, 1976; Pouwels, 1978a,b), as well as other teleosts (e.g., Finger, 1983; Murakami & Morita, 1987). Eurydendroid cells have their cell body in the layer of Purkinje cells (hence also termed ganglionic layer in teleosts), and broadly extending (i.e. eury-) dendrites in the molecular layer (Nieuwenhuys et al., 1974; Pouwels, 1976). The main difference with Purkinje cells, apart from their different axonal projections, concerns the fact that eurydendroid dendrites make aspiny instead of spiny synaptic contacts with parallel fibers (Meek & Nieuwenhuys, 1986). The presence of eurydendroid projection neurons in the teleostean cerebellum means that teleostean Purkinje cells are interneurons, not projecting outside the cerebellar cortex, but within the ganglionic layer on neighbouring Purkinje, eurydendroid and deeply located stellate cells (Meek & Nieuwenhuys, 1991).

2 main differences:
① central cerebellar nuclei absent in teleosts

Purkinje cells = interneurons

A second difference in the extrinsic connectivity of the teleostean cerebellum compared with tetrapods concerns the presence of a specialized precerebellar nucleus, termed nucleus lateralis valvulae, just like the valvula cerebelli only present in actinopterygians. This nucleus gives rise to important mossy fiber projections to the teleostean cerebellar granule cells, not only in the valvula, but also in the corpus cerebelli (Finger, 1983; Meek et al., 1986a,b; Wullimann & Northcutt, 1988, 1989; Ito & Yoshimoto, 1990). The nucleus lateralis valvulae is located in the midbrain tegmentum and consists of adendritic cells that receive input from a variety of sources (Meek et al., 1986a,b; Ito & Yoshimoto, 1990). Thus, in teleosts a particular precerebellar nucleus is involved in cerebellar input, while a central cerebellar nucleus, involved in cerebellar output, is absent (Fig. 3).

② nucleus lateralis valvulae

With respect to the intrinsic organization of the teleostean cerebellar cortex a rich variety presents itself, contrasting with the apparent rigidity of the tetrapodian cerebellar organization. For instance, the teleostean cerebellum is not always trilaminar, since neither Purkinje cells nor granule cells are always located in a layer. Purkinje cells may equally well be dispersed in the molecular layer (Fig. 2) and granule cells may be located

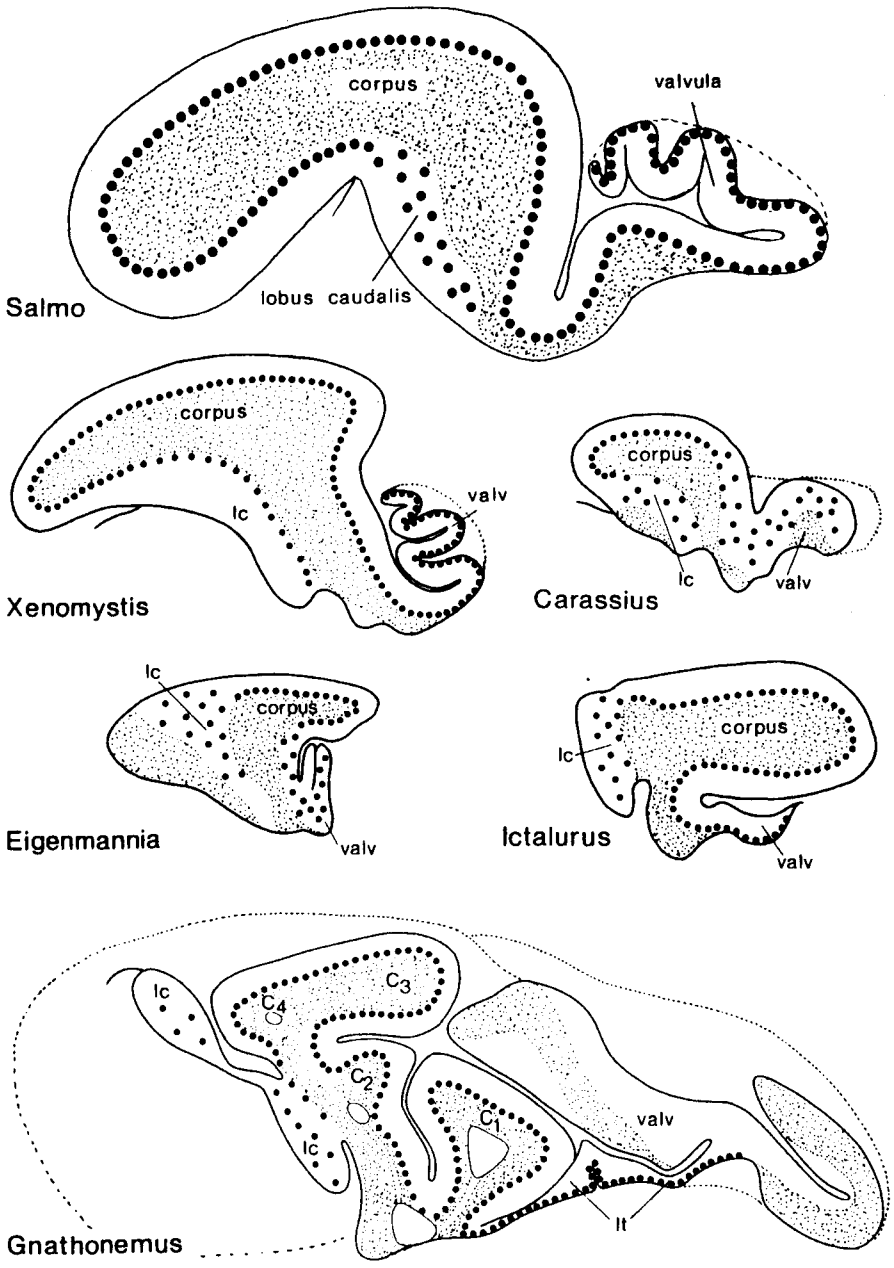

Fig. 2. Midsagittal reconstructions of the cerebella of a variety of teleosts. A lateral view of the first one (Salmo) and the last one (the mormyrid fish Gnathonemus) is presented in Figure 1. This figure gives an impression of the variability encountered in teleost with respect to the size and shape of the valvula as well as the corpus cerebelli, and the location of Purkinje cells either in a monolayer or distributed in the molecular layer. Purkinje cells are indicated by large dots, granule cells by small stipples, while the molecular layer is left unshaded. C_1-C_4 indicate the mormyrid cerebellar lobes C_1-C_4; lc = lobus caudalis; lt = lobus transitorius; valv = valvula cerebelli. Magnification: 15x.

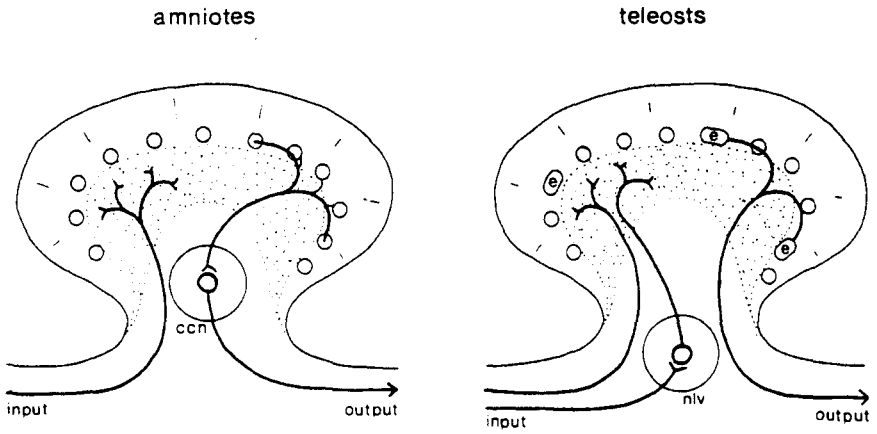

Fig. 3. Summarizing scheme of some basic differences in the organization of extrinsic cerebellar connections in teleosts and amniote tetrapods (i.e. mammals, birds and reptiles). For further details, see text. ccn = central cerebellar nucleus; e = eurydendroid cell; nlv = nucleus lateralis valvulae.

lateral instead of basal to the molecular and Purkinje cell layer, giving rise to parallel fibers without a T-shaped bifurcation (Meek, 1992). In this respect the elasmobranch cerebellum is also noteworthy, since here the granule cells are concentrated in two longitudinally oriented ridges, the prominentiae granulares (Nicholson et al., 1969; Smeets et al., 1983). The organization of Purkinje cells in teleosts differs from mammals with respect to the location of the so-called 'smooth' part of the dendritic tree, which is in teleosts restricted to the proximal part of the dendritic tree, whereas it penetrates the molecular layer in mammals (Fig. 4). Since this 'smooth' part represents the receptive surface for climbing fibers, these do not seem to penetrate the molecular layer in teleosts, but to terminate exclusively on the proximal dendrites of Purkinje cells within the ganglionic layer (Fig. 4). Although this has only been convincingly demonstrated for mormyrid teleosts (Meek & Nieuwenhuys, 1991), it is probably also the case in other teleosts, including trout (Pouwels, 1976) and catfish (Finger, 1983). Most likely, a one to one relation between olivocerebellar 'climbing' fibers and Purkinje cells is equally absent in teleosts, since two or more different olivocerebellar fibers may converge upon the receptive surface of Purkinje cells (Meek & Nieuwenhuys, 1991). At last, it may be noticed that basket cell are absent in teleosts (e.g., Pouwels, 1976; Finger, 1983; Meek & Nieuwenhuys, 1991), which means that inhibitory feedback loops are only established by Golgi- and stellate cells.

basket cells absent in teleosts

Recent immunohistochemical studies have shown that a parasagittal zonation, which is characteristic for the mammalian cerebellum, is largely absent in teleosts (Brochu et al., 1990; Meek et al., 1992). This is due to the fact that the teleostean cerebellum is basically a quite narrow sheet of tissue, as shown clearly by a topological analysis according to Nieuwenhuys (1974) of the cereballar surface (Fig. 5). Apparently, the teleostean cerebellum represents at most places a single cerebellar zone with a narrow width, restricting parallel fiber length, and without a further parasagittal zonation, in contrast to the mammalian cerebellum, where the transverse dimensions do not restrict

parasagittal zones mostly absent

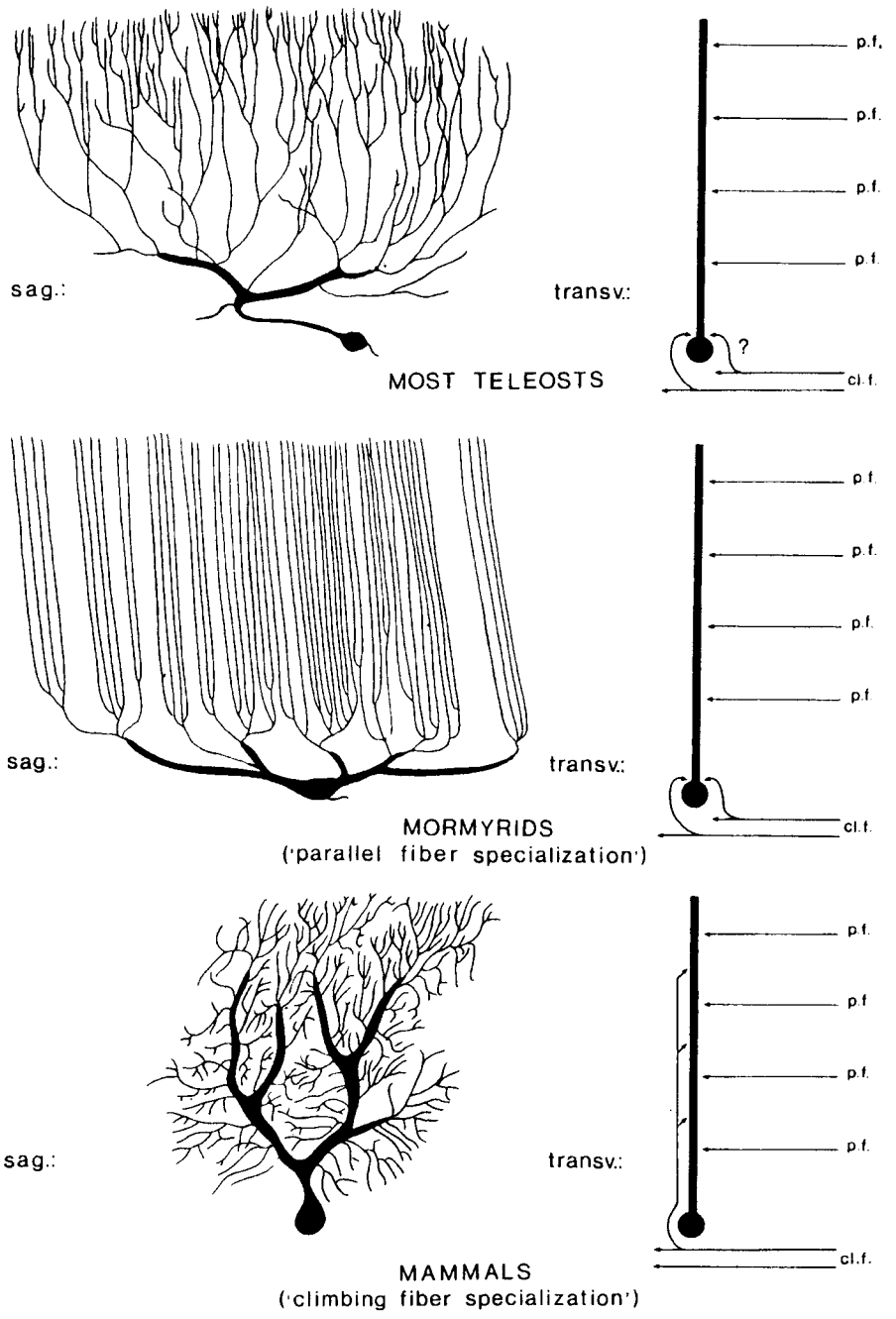

Fig. 4. Some characteristics of teleostean (including mormyrids) and mammalian Purkinje cells, showing their overall dendritic organization in the sagittal (sag) plane, and their connectivity pattern with parallel fibers (pf) and climbing fibers (cl.f) in the transverse (transv) plane. In the sagittal views, the so-called 'smooth', climbing fiber receptive surface has been drawn thick. The spiny dendritic compartment, making numerous spiny synaptic contacts with parallel fibers, has been drawn thinly, without the spines. For further details, see text.

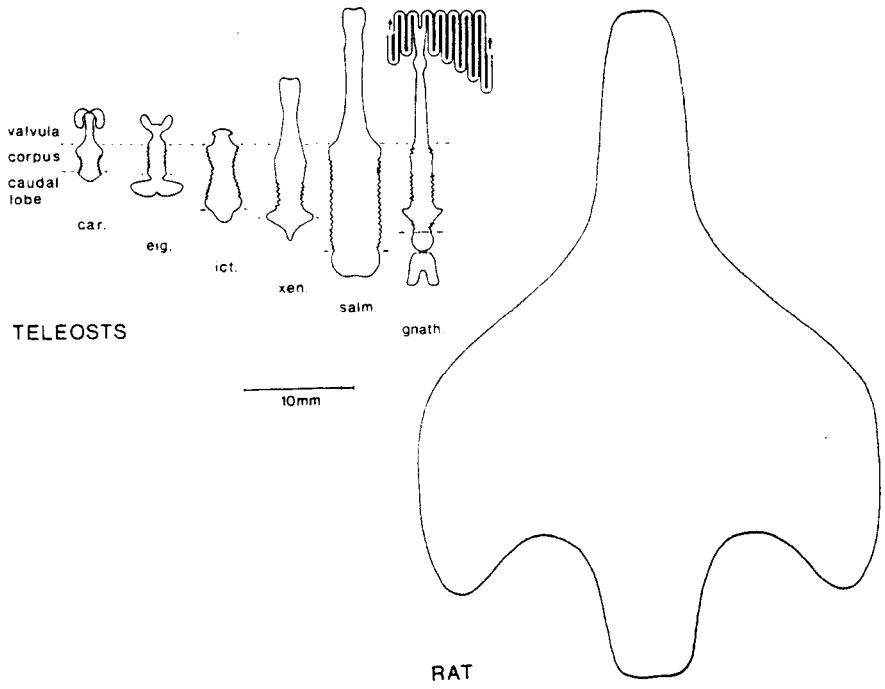

Fig. 5. Topological reconstructions of the unfolded, flattened surface of the teleostean cerebella also shown in figure 2, compared with a similar reconstruction of the cerebellar cortex of the rat, according to the method described by Meek et al. (1992). This figure shows that the teleostean cerebellum is basically a rather narrow zone of cerebellar tissue, with a width restricting parallel fiber length. This contrasts markedly with the mammalian cerebellum with its dramatically larger width, not restricting parallel fiber length (see text for further details).

parallel fiber length, and many zones are juxtapositioned in the transverse plane (Fig. 5; Meek et al., 1992).

TELEOSTEAN CEREBELLOID STRUCTURES

The degree of variability and deviation from the 'basic cerebellar circuitry' described above for the teleostean cerebellum becomes still larger when one takes two teleostean cerebelloid structures into consideration, i.e. structures not belonging but still related to the cerebellum, and with a cerebellum-like organization. These are the cerebellar crest, located just caudal to the caudal cerebellar lobe, and the torus longitudinalis, located just rostral or dorsal to the valvula.

The cerebellar crest is a layer of parallel fibers covering the lateral line primary sensory brain stem region, originating from a paired mass of granule cells located caudolaterally to the caudal cerebellar lobe and termed the granular eminence (Nieuwenhuys, 1967; Larsell, 1967). The parallel fibers contact the spines of Purkinje-like cells, termed

crest cells, located at the interface between the cerebellar crest and the lateral line nucleus. Peculiar aspects of this cerebelloid configuration include the fact that parallel fibers do not run in the transverse but in the rostrocaudal direction and enter the molecular layer (or cerebellar crest) from only one direction. In this way they give rise to a unidirectional molecular layer, in which all parallel fibers conduct signals in one and the same direction (Meek, 1992). The dendrites of Purkinjoid crest cells are not oriented in a plane perpendicular to the direction of parallel fibers, as is always the case in intracerebellar molecular layers, including those of teleosts (see Meek, 1992).

The torus longitudinalis is a paired ridge of granule cell located along the medial boundary of the teleostean tectum, projecting its parallel fibers over the surface of the midbrain tectum in the so-called marginal layer (see Meek 1983 and 1992 for review). It receives its input predominantly from the valvula cerebelli and is, just like the latter structure, only present in actinopterygian fishes. It shows the same peculiarities as the cerebellar crest system just described, including unidirectional parallel fibers, in this case with a medio-lateral direction, and a non-perpendicular orientation of the spiny dendritic trees of the recipient neurons, in this case large fusiform or type I neurons with a cell body in the retinorecipient layer of the teleostean tectum (Meek, 1983). In addition, stellate cells or other neurons establishing inhibitory feedback loops, still present in the cerebellar crest system (Carr & Maler, 1986; Bell & Szabo, 1986), seem to be absent in the teleostean torus longitudinalis-tectal marginal layer system (Meek, 1983, 1992). It should be noticed that both in the cerebellar crest and the tectal marginal layer olivocerebellar ('climbing') fibers are absent. Instead, the spiny target cells of parallel fiber synaptic contacts receive primary sensory input (lateral-line and visual, respectively) on their somata and/or basilar dendrites, either directly or indirectly (see Carr & Maler, 1986; Bell & Szabo, 1986; Meek, 1983).

THE MORMYRID CEREBELLUM

The cerebellum of mormyrid teleosts is already for a long time well known for its gigantic size (Stendell, 1914), encompassing about 1% of the total body weight of these fishes (Meek & Nieuwenhuys, 1991), a value not approximated in any other vertebrate, including mammals (Figs. 1, 2). This is largely due to the huge outgrowth of the valvula cerebelli, which covers the complete dorsal aspect of the brain in these fishes. The mormyrid gigantocerebellum has for more than 25 years enjoyed the continuous interest of Nieuwenhuys, who unravelled a large number of interesting aspects of this intriguing cerebellum in collaboration with Nicholson, Pouwels and Meek, respectively (e.g., Nieuwenhuys & Nicholson, 1967, 1969a,b; Nieuwenhuys et al., 1974; Nieuwenhuys, 1976; Meek & Nieuwenhuys, 1986, 1991; Meek et al., 1986a,b, 1992; Meek, 1992).

Although the cerebellum of mormyrids is larger than that of other teleosts, it is typically teleostean in the sense that all specializations and variations described above are present in the mormyrid cerebellum. Accordingly, a valvula, corpus and caudal lobe can be distinguished, however, with a further, more refined subdivision. The valvula consists not only of the valvula strictiori sensu, a plate of granule cells on which ridges of Purkinje cells and granule cells are oriented perpendicularly, but in addition the lobus transitorius and lobe C_1 (Fig. 2) belong to the valvula (Meek et al., 1992). The corpus cerebelli of mormyrids is differentiated into three distinct lobes: C_2 and C_3 directed rostrally and C_4 directed caudally. The caudal lobe is differentiated into an anterior part, attached

to the mechanosensory lateral line lobe, and a posterior part, attached to the electrosensory lateral line lobe (Bell & Szabo, 1986; Meek, 1992).

The extrinsic connections of the mormyrid cerebellum also follow the rules described above for other teleostean cerebella: there are well-differentiated eurydendroid or giant cells (Nieuwenhuys & Nicholson, 1969b; Nieuwenhuys et al., 1974), projecting to a number of premotor regions (Meek et al., 1986a,b), and there is a highly differentiated precerebellar nucleus lateralis valvulae. The latter consists of a large number of subdivisions, each of which projects to specific parts of he valvula and corpus of the mormyrid gigantocerebellum (Meek et al., 1986a,b). Mormyrid climbing fibers equally terminate only on the proximal parts of Purkinje cell dendrites (Fig. 4; Meek & Nieuwenhuys, 1991), and a parasagittal zonation is largely absent in the mormyrid cerebellum (Fig. 5; Meek et al., 1992).

Apart from its large size, the most outstanding feature of the valvula as well as the corpus cerebelli of mormyrids is the presence of a palisade pattern in the molecular layer. This was discovered by Nieuwenhuys & Nicholson (1967, 1969a,b), and is caused by the specific configuration of the Purkinje cell dendrites: these run mostly unbranched from deep to superficial in the molecular layer, densely occupied with spines (Fig. 4). In spite of careful observations at the light and electron microscopical level, we could not find specific morphological or synaptic properties of Purkinje cells that are correlated with this palisade pattern and thus might point to its possible functional significance (Meek & Nieuwenhuys, 1991). This had led us to the suggestion that the palisade pattern might be considered as a specialization to extract optimal information from patterned parallel fiber input, whereas on the other hand the mammalian configuration might be considered as an adaptation for optimal interactions between cerebellar parallel fiber and climbing fiber input (see Fig. 4).

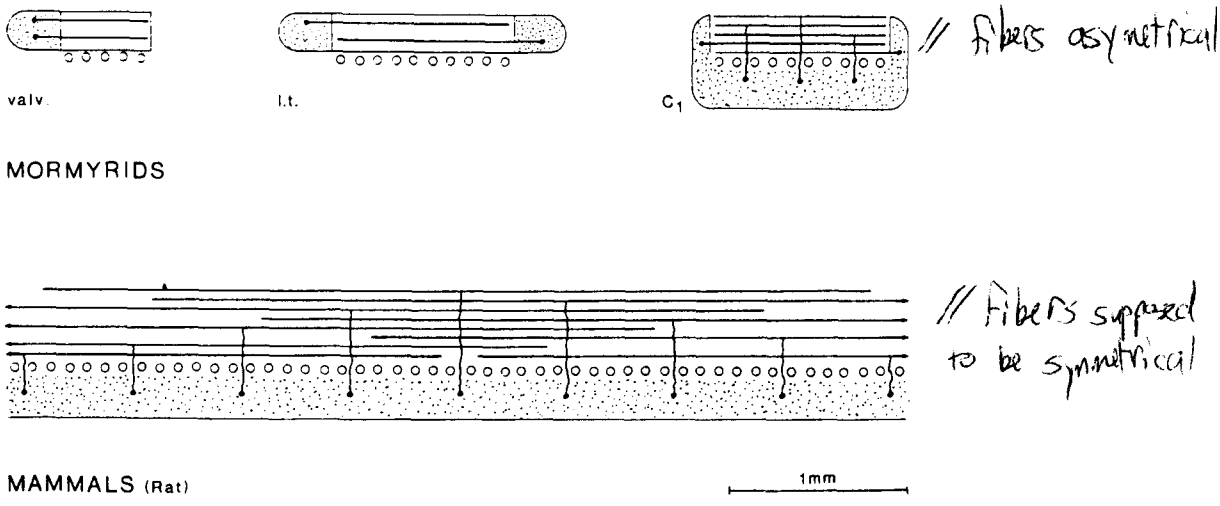

Fig. 6. Transverse views of the granule cell – parallel fiber – Purkinje cell configurations encountered in the mormyrid valvula cerebelli (valv), lobus transitorius (l.t.) and lobe C_1, compared with the mammalian one.

With respect to the location of granule cells and the configuration of parallel fibers, the mormyrid cerebellum shows clear examples of all possibilities encountered in other teleosts (Fig. 6). In the rostrally located valvula (strictiori sensu), the ridges of molecular layer and Purkinje cells are located perpendicular to the granule cell layer (Nieuwenhuys & Nicholson, 1969a), which means in fact that the granule cells are located lateral to the molecular layer, at only one side, giving rise to unbranched, non-bifurcating parallel fibers in a unidirectional molecular layer, where parallel fibers all conduct signals in the same direction. A similar situation is present in the torus longitudinalis-marginal fiber system described above, but here the parallel fibers may be 5 mm or even longer, whereas those in the mormyrid valvula are only about 0.5 mm long (Fig. 6). In the lobus transitorius, granule cells are located at both sides of the molecular layer (Nieuwenhuys & Nicholson, 1969a), also giving rise to unidirectional parallel fibers, however in a bidirectional molecular layer, since at any place both fibers running from left to right and vice versa are present (Fig. 6; Meek, 1992). In lobe C_1, this configuration is combined with basally located granule cells, giving rise to bifurcating parallel fibers. Remarkably, most of the latter are asymmetrically, i.e. with a left and right branch of unequal length, since all parallel fibers are of equal total length and coextensive in the transverse plane (Meek & Nieuwenhuys, 1991). This situation deviates significantly from the mammalian one, where all parallel fibers are supposed to be symmetrical (Fig. 6).

FUNCTIONAL CONSIDERATIONS

The survey just presented shows that the one and only constant characteristic of vertebrate cerebellar and cerebelloid cortices is the presence of numerous thin, unmyelinated fibers with a parallel course that originate from granule cells with mossy fiber input, and that contact spiny dendrites. Consequently, the concept of a 'basic cerebellar circuitry' should be restricted to this single feature. All other aspects are variable and may be absent, including a trilaminar organization of the cerebellar cortex, the presence of bifurcating parallel fibers, an orthogonal orientation of the recipient spiny dendritic trees, climbing fiber input, inhibitory feedback loops, etc. This restriction of the 'basic cerebellar circuitry' to the parallel orientation of parallel fibers, together with our idea that the mormyrid palisade pattern represents a specialization for optimal detection of specific patterns of parallel fiber input, has recently resulted in the formulation of a coincidence detection-hypothesis (Meek, 1992). The following may be noticed in this respect.

Most concepts on mammalian cerebellar functional organization (see Ito, 1984 and Meek, 1992 for refs.) start implicitly or explicitly from the idea that cerebellar signal processing is spatially specified, in the sense that each Purkinje cell receives a specific set of inputs, different from its neighbours, just as in other topographically organized brain regions as the midbrain tectum and telencephalic neocortex. This is induced by the topographic (although complex and patchy) organization of both mossy and climbing fiber cerebellar input and the general assumption that mammalian parallel fibers branch symmetrically (e.g., Ito, 1984), which indeed would yield a situation in which all Purkinje cells receive different, although overlapping, parallel fiber inputs. In fact, most concepts only consider the proximal effects of parallel fiber activity, and thus assume that Purkinje cell activity induced by parallel fiber activity largely reflects mossy fiber input on the granule cells located just underneath each Purkinje cell.

The examples shown in Figure 6 clearly demonstrate that this cannot be true for the

teleostean cerebellum with its narrow cortex and coextensive parallel fibers. For, all Purkinje cells at a certain rostrocaudal level located next to each other receive input from exactly the same set of parallel fibers, without any spatial differentiation. The only difference encountered in parallel fiber activation of Purkinje cells is a temporal one, since Purkinje cells contacted by the proximal part of a parallel fiber will be activated earlier than Purkinje cells contacted by more distal parts of that parallel fiber. This brings us back to the idea of Braitenberg (Braitenberg & Onesto, 1961; Braitenberg, 1967), that parallel fibers should be considered as delay lines, and the cerebellar cortex as a timing device.

The cerebellar configurations of mormyrids represent nice examples to illustrate how a cerebellar timing function might work. For instance, in the lobus transitorius (see Fig. 6), parallel fiber activity waves running from left to right as well as from right to left may be generated by mossy fiber activity. When both waves are generated simultaneously, they will meet in the midline region, resulting in maximal stimulation of Purkinje cells in this region. However, when the left wave is generated more early than the right waves, Purkinje cells located at the right side of the midline will be stimulated maximally. The exact place of maximal Purkinje cell stimulation thus depends on the precise time difference in activation of the left or right granule cell mass. This means that Purkinje cells may be considered as coincidence detectors of parallel fiber input, and the lobus transitorius as a timing device subserving spatial coding of temporal differences in mossy fiber input. Starting from this example, it appears that similar mechanisms may underlie coincidence detection in unidirectionally organized molecular layers, as encountered in the mormyrid valvula (Fig. 6) or the teleostean torus longitudinalis-marginal fiber system, on the basis of two populations of parallel fibers with slightly different conduction velocities, as was indeed demonstrated in the teleostean tectum (Vanegas et al., 1979). In cerebellar cortices with basally located granule cells, including the mormyrid lobe C_1 (Fig. 6) as well as the mammalian cerebellum (Fig. 6), similar mechanisms might well subserve the analysis of more complex, specific spatiotemporal mossy fiber input waves (Meek, 1992).

The hypothesis on coincidence detection of parallel fiber activity appears to be compatible with, and to provide clues for the explanation and integration of many well known data. For instance, the plastic attenuative properties of cerebellar spines (Sakurai, 1989), as well as the properties of the inhibitory feedback loops (Eccles et al., 1967; Ito, 1984) all seem to optimize coincidence detection by Purkinje cells, while the heterosynaptic activity of climbing fiber input and parallel fiber input processing (Bloedel & Zuo, 1989) might well be involved in the attenuation or enhancement of coincidence detection at certain cerebellar sites or zones, depending on the position or phase of movement of the animal at any time (Meek, 1992). The coincidence detection hypothesis also throws a new light on the cerebellar function in sensory-motor integrative processes. Because of the motor deficits observed after cerebellar lesions or dysfunction, the cerebellum is generally considered as a part of the motor-control system (Dow & Moruzzi, 1958; Ito, 1984). However, comparative analysis of the teleostean cerebellum and implementation of the coincidence detection hypothesis on the mammalian cerebellum strongly suggest that the cerebellar cortex is basically a sensory, i.e. a signal analyzing structure, and not a signal integrating or premotor structure. The latter function is most likely subserved by the next stages in cerebellar circuitry, i.e. the cerebellar nuclei or the teleostean eurydendroid output cells and their targets. The present comparative analysis strongly suggests that a better understanding of cerebellar function can be achieved when the cerebellum is not exclusively considered as a center for motor control, but when the important signal-

analyzing properties of the parallel- fiber- Purkinje cell interactions in the molecular layer are incorporated as well in future concepts.

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