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The Embryonic Development of the Cerebellum in Normal and Reeler Mutant Mice

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Summary. The development of the cerebellum has been studied in normal and reeler mice, from embryonic day fourteen, i.e. when morphogenesis begins in this organ, to birth. The cerebellar nuclei develop according to a similar sequence in both genotypes. Their neurons migrate into the rostral field of the cerebellar bud where they condense in a rounded mass, well defined at E14. From E17, this cell contingent spreads transversally and the three roof nuclei become clearly defined. In reeler mutants, there seems to be an abnormal development of the architectonics of the lateral nucleus. The Purkinje cells migrate into the cortex at the same time in both genotypes. In the normal animal, from E14 onward, Purkinje cells are condensed in a clearly defined plate, where they assume a radial organization. By contrast, the mutant Purkinje cells are not arranged in a plate but are scattered in the periphery of the cortex. The neurons of the external granular layer are identical in both genotypes. Radial glial fibers and early Golgi epithelial cells appear to be normally present in the reeler embryo. The foliation of the cerebellar cortex begins at E17 in the normal embryo. From this stage onward, foliation is increasingly deficient in reeler mutants. Based on these observations, it is suggested that, in normal cerebellar development, a specific, genetically determined mechanism is responsible for the organization and the stabilization of postmigratory neurons and that this mechanism is affected by the reeler mutation.

Key words: Cerebellum – Histogenesis – Mouse – Reeler mutation

Introduction

The gross development of the mammalian cerebellum largely occurs after birth. This is particularly so regarding the migration of granule cells, which

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has been extensively studied (e.g. Rakic 1971). Many events of cerebellar histogenesis, however, are well advanced at birth, as appears from the pioneering study of Tello (1940) and from the more recent works of Korneliussen (1967, 1968), Rakic and Sidman (1970), Zecevic and Rakic (1976), Altman and Bayer (1978), Swarz and Oster-Granite (1978). More specifically in mice, a Purkinje cell stratum (two to four cells thick), the central cerebellar nuclei and the four main folia are well defined at birth.

The reeler mutation in mice leads to a well-studied malformation characterized by a nearly complete absence of foliation and heterotopy of Purkinje cells (Rakic 1976; Mariani et al. 1977; Steindler 1977; Sotelo and Privat 1978; Wilson et al. 1981). The mutant phenotype can be traced back to the embryonic period, as mentioned by Caviness and Rakic (1978), and thus provides us with an experimental probe in prenatal cerebellar development. In order to obtain a better understanding of the mechanisms involved in cerebellar development, and especially of some genetic determinants of its organization, a comparative morphological analysis of cerebellar histogenesis has been performed in normal and reeler mice, from embryonic day 14 to birth.

Materials and Methods

Animals. The Oreleans allele of the reeler mutation (rl Orl) was originally provided by Dr. J.L. Guenet (Institut Pasteur, Paris). The mutation is maintained on a recombinant 129/Sv × BALB/c background. Embryos are obtained by mating fertile homozygous males with heterozygous females. The day a vaginal plug is formed is noted as day zero (E0). Heterozygous embryos are normal, and have been taken as controls (referred to as normal control animals in the text). A total number of 57 embryonic litters was used for the present analysis.

Embryological Analysis. Embryos were fixed by immersion (until E17) or by intracardiac perfusion with Bouin Hollande fixative (Gabe 1968), and the heads or the dissected brains (from E18 onward) were embedded in paraplast. Serial sections were cut in the frontal plane at 10 μm, and stained with hematoxylin-eosin.

Golgi Method. Embryos were fixed by intracardiac perfusion by gravity flow (60 cm), using a 26 G needle. The fixative was composed of 4% formaldehyde, 1% glutaraldehyde and 0.1 M phosphate buffer, pH 7.4–7.6. The heads were postfixed overnight at 4° C in the same mixture, rinsed (3 × 15 min) in phosphate buffer and placed in chromate solution (3% $K_2Cr_2O_7$; 0.25% OsO_4) at 4° C for from three to seven days. They were subsequently rinsed and impregnated with silver nitrate (0.75% in distilled water), embedded in celloidin and cut serially in the frontal plane at 100–150 μm. Drawings were made with a drawing tube, using an immersion objective (× 50 or × 100).

Results

In our mouse strain, the cerebellar anlage appears at E12, as a neuroepithelial swelling of the rostral lip of the fourth ventricle. Before E14, the cerebellum is poorly differentiated and no distinction can be made between normal and reeler littermates. In the present description, three developmental stages will be described, namely: 1) the early cerebellar organization (corresponding to E14–E15), 2) an intermediate stage when the central nuclei divide

into three components and when the first fissure is seen (E17), and 3) the newborn stage.

Early Cerebellar Histogenesis: E14–E15

Normal Embryos. The cerebellum at E14–E15 is composed of two symmetrical primordia, in continuity with each other by a thin commissure at the level of the raphe (Fig. 1). Among the several cell populations which are found at this stage, a prominent ventricular zone (VZ) covers the ventricular surface and is populated by proliferating cell precursors. Its morphological features are similar to what has been described elsewhere (Hinds and Ruffett 1971; Swarz and Oster-Granite 1978). The external processes of the ventricular cells run radially through the whole thickness of the tissue and correspond to the "radial glial fibers" well visible in Golgi impregnated material (Fig. 2). Externally to the VZ, the intermediate zone (IZ) mainly contains radially migrating cells. In the medial and rostral field of the cerebellar bud, two paired masses of large, young neurons are seen (Fig. 1). Their nuclei are ellipsoidal (12–15 μm to 5 μm) and contain a fine, reticular chromatin. The sparse cytoplasm is bipolarly distributed. This cell contigent corresponds to the neurons of the central cerebellar nuclei and has been described as migratory component A (migr A) by Rüdeberg (1961) and by Korneliussen (1967, 1968). All around this cell mass, i.e. laterally and caudally, the cerebellar cortex is composed of four concentric layers extending from the pial surface to the intermediate zone, namely the external granular layer (EGL), 25 μm thick, the marginal zone (MZ, 25 μm), the Purkinje cell layer (PP, 25 μm) and a thin cell-poor zone, here named the sub-Purkinje plate or subPP (Fig. 1c, e). The EGL appears when the first Purkinje cells reach their position in the cortex, and is about 3 to 4 cells thick. External granule cells at that stage have polymorphic features. Near their site of origin, at the lateral recess of the fourth ventricle, their nuclei are quite large and ellipsoidal (long axis 8–10 μm), but they become smaller and nearly spherical (diam. 5 μm) at the rostral level of the EGL – at the front of the tangential wave of migration. Golgi-impregnated granule cells are at the stage of the "bipolarité horizontale" (Cajal 1911). Beneath the EGL, a fiber-rich, cell-poor layer is defined. It corresponds to the incipient MZ and covers the layer of Purkinje cells. The Purkinje cells are arranged in a pluricellular plate (6 to 8 cells thick) and have a radial organization and a polarized differentiation. Their nuclei are radially elongated, ranging from 6 to 8 μm in diameter. The nuclear features are more uniform than those of external granule cells. The radial arrangement of Purkinje cells is seen for the first time at E14 (Fig. 1) and becomes very clear at E15 (Fig. 1). This transient organization of Purkinje cells is named the Purkinje plate (PP) by analogy to the telencephalic cortical plate (CP: Boulder Committee 1970). The Golgi impregnation reveals the polarization and the radial organization of normal Purkinje cells (Fig. 2b). The external, apical dendrites divide like "bouquets" into two to four tributaries. The axons originate from the internal cell poles and run into the IZ. Although a growth

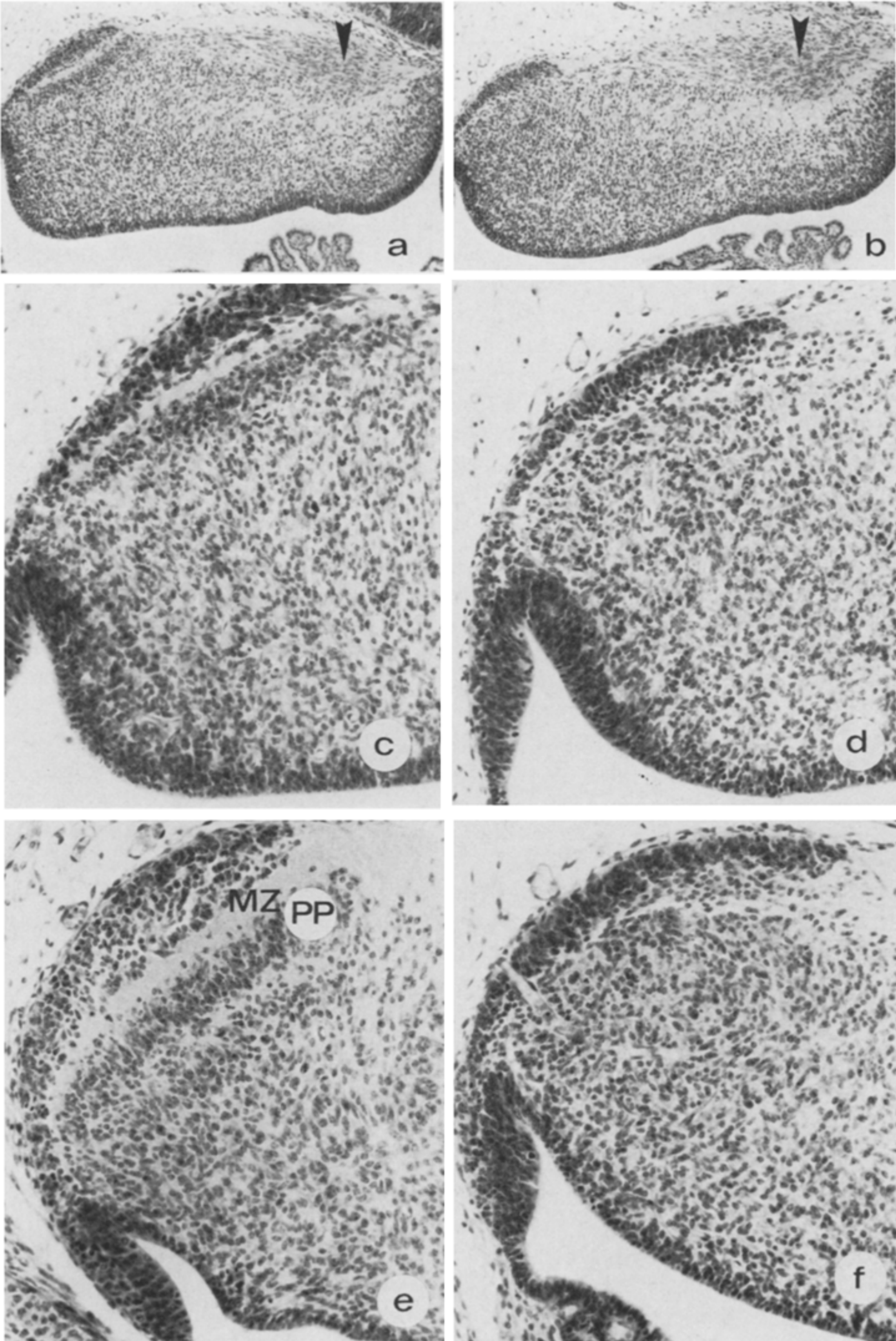

Fig. 1 a–f. The early stage of cerebellar histogenesis: embryological analysis. **a, b** low-power view of the cerebellum at E14 in normal (**a**) and reeler (**b**) embryos. The mass of central nuclei is shown by the arrowhead (×55). **c, d** the cerebellar cortex at E14 in normal (**c**) and reeler (**d, e**) embryos (×150). **e, f** the cerebellar cortex at E15 in normal (**e**) and reeler (**f**) embryos. *MZ* marginal zone; *PP* Purkinje plate (×150)

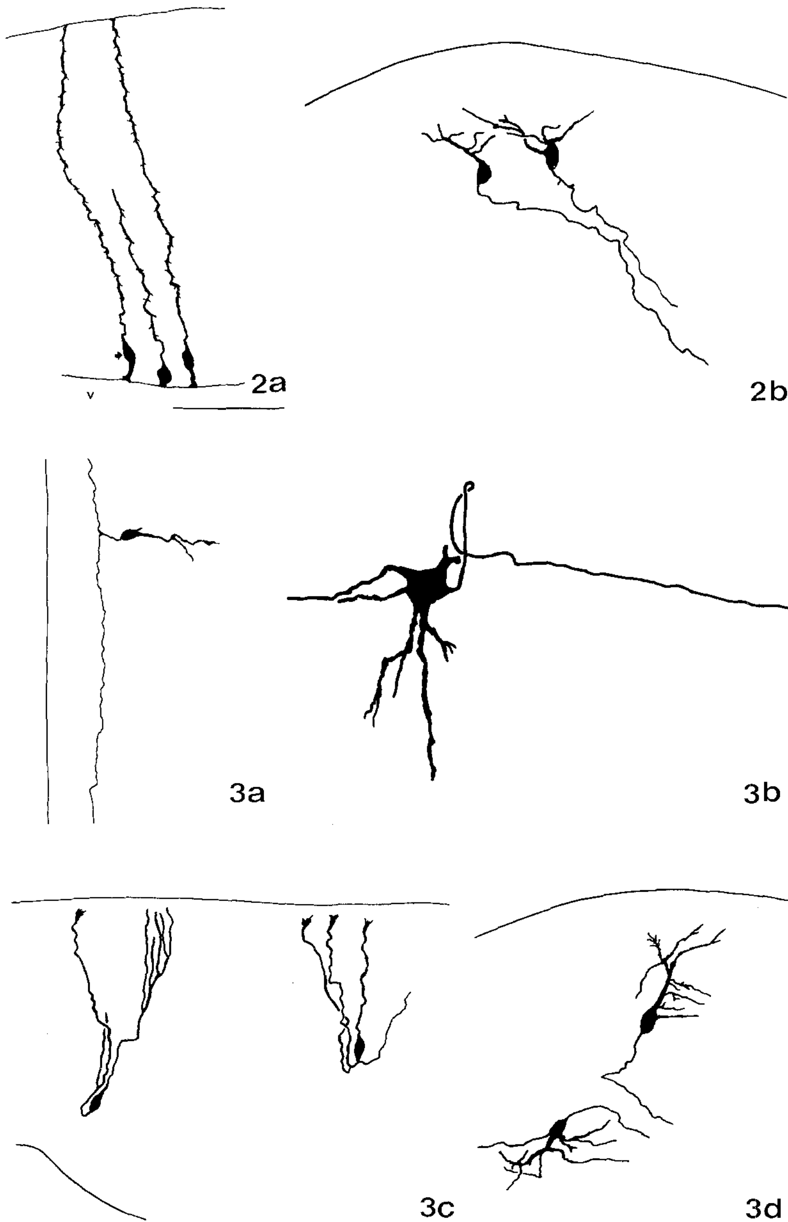

Fig. 2a–b. The early cerebellum: Golgi study. **a** At E14, radial glial cells extend from the ventricle (*V*) to the pial surface (×160). **b** Two neurons in the normal Purkinje plate at E14 (×280)

Fig. 3a–d. The cerebellum at E17: Golgi impregnation. **a** External granule cell engaged in radial migration (×190). **b** Neuron of the central cerebellar nucleus with a twisted initial axonic segment (×480). **c** Two Golgi epithelial cells with radial extensions corresponding to early Bergmann fibers (×200). **d** Two Purkinje cells in the reeler cortex, one normally oriented, the other inverted (×190)

cone is sometimes visualized at their extremity, we were usually unable to follow them to their extremity. A thin, fiber-rich layer is formed just beneath the PP. It is poorly developed at E14 but becomes obvious at E15 and corresponds to the future "lamina dissecans" (Rakic and Sidman 1970). Again, by analogy to the nomenclature used for the cerebral cortex (Pinto-Lord and Caviness 1979), we refer to this embryonic layer as the sub-Purkinje plate (subPP). Deeper in the cerebellar primordium, between the subPP and the ventricle, the large intermediate zone is populated with poorly differentiated cells presumably engaged in radial migration, as studied by Swarz and Oster-Granite (1978).

Reeler Mutant Embryos: (Early Stage). The reeler phenotype is first expressed in the cerebellar cortex at E14. The mutant cerebellum is of normal size and contains the same components as its normal counterpart (Fig. 1). The VZ, IZ, central nuclei and EGL appear normal. However, beneath the EGL, the MZ is absent or at least poorly defined, the Purkinje plate is defective and no obvious limit can be drawn between the Purkinje cell population and the contingent of cells engaged in radial migration (Fig. 1). In the absence of suitable markers, it is difficult to ascertain the presence of the Purkinje cells. Even the Golgi method does not allow a clearcut identification of these elements in the reeler cerebellum at this stage. Immature neuronal cells with features very suggestive of embryonic Purkinje cells are localized at the external part of the cortex. At E15, when the normal PP is well organized, the reeler malformation becomes increasingly manifest (Fig. 1). The elements presumed to correspond to Purkinje cells are dispersed at the external limit of the intermediate zone.

Late Embryonic Stage: E17

Normal Embryos. By comparison with the previous stage, E17 is characterized by the tangential growth of the cerebellar cortex and by the concomitant spreading and subdivision of the central nuclei (cfr. Fig. 4). The tangential growth of the cortex proceeds in all directions, but mainly rostrally. The external granular layer is populated with bipolar neurons, some of which appear to begin their inward migration and are at the stage of the "bipolarité verticale" (Cajal 1911; Fig. 3a). In the Purkinje plate and the MZ, the apical dendritic tree of the Purkinje cells ramifies into several branches (up to five) which run through the MZ. The axon invariably leaves the internal pole of the cell and enters the IZ where it is usually lost; sometimes a growth cone is seen capping the extremity. The first evidence for a cortical foliation is found at E17, as a notch in the PP. The notch occurs always at a point where radial vascular arches enter the parenchyma (radial perforating vessels are present from E12–E13). The process of cortical foliation is first seen in the depth of the cerebellar cortex, at the level of the PP, before it affects the MZ and the cerebellar surface. The mass movement of the cortex occurs in parallel to a translocation of the central nuclei towards the depth of the parenchyma, and to their spreading in the transversal

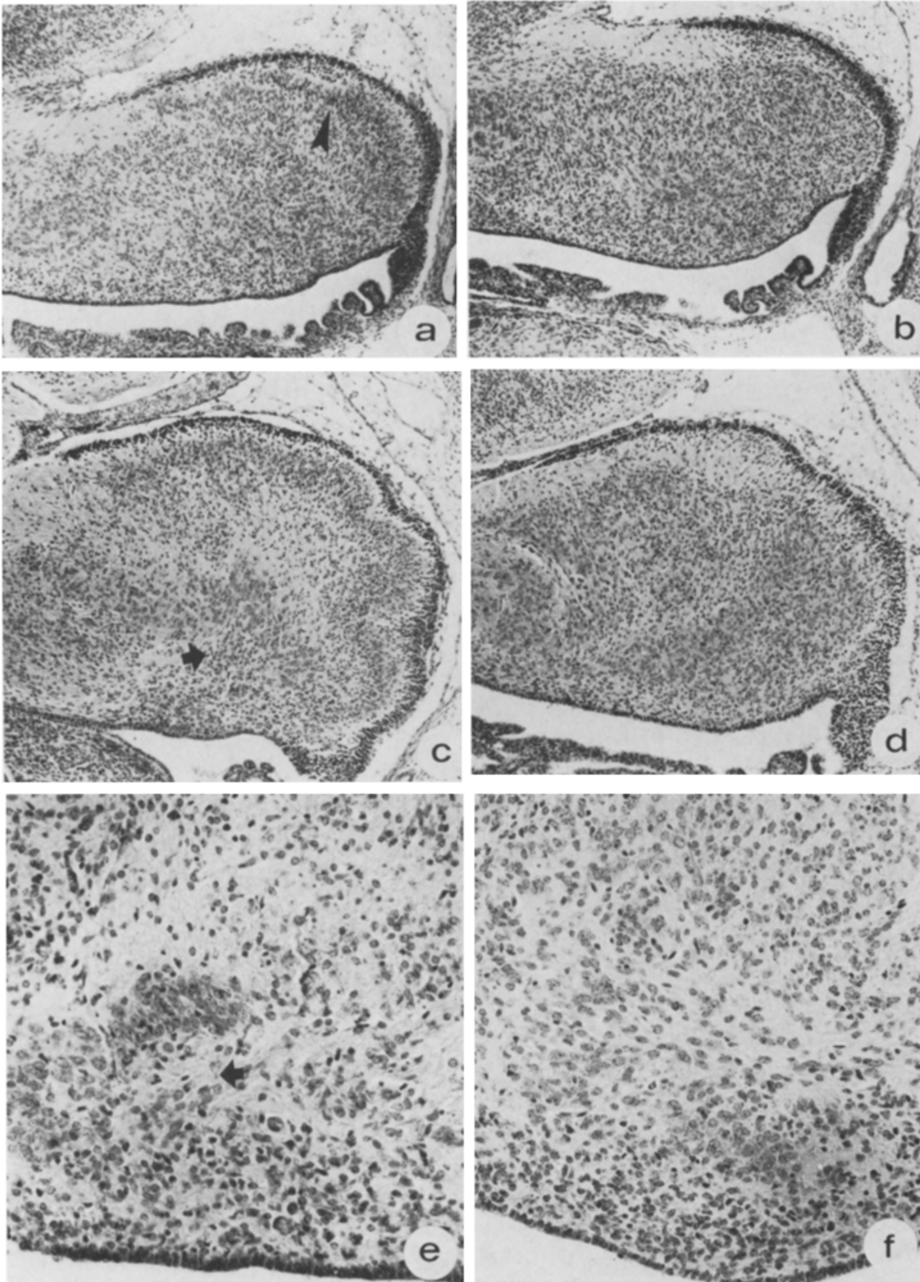

Fig. 4a–f. Cerebellar development: late embryonic stages. **a**, **b** Frontal sections in a normal (**a**) and reeler (**b**) cerebellum at E17. In the normal specimen, a notch (*arrowhead*) is present at the level of the future fissura prima (×55). **c**, **d** Frontal sections in the cerebellum of normal (**c**) and reeler (**d**) newborn. The *arrow* on (**c**) points to the hilus of the lateral nucleus. **e**, **f** The lateral cerebellar nuclei of normal (**e**) and reeler (**f**) newborn mice. The *arrow* on (**e**) points to the normal hilus, which is poorly defined in the reeler nucleus (**f**) (×140)

plane. At that stage, the central nuclei begin to separate into three components, still incompletely defined: the medial; intermediate and lateral cerebellar nuclei. The cells of the roof nuclei display a characteristic morphology of well differentiated, multipolar neurons (Fig. 3b). The dendritic ramifications radiate around the cell body, usually in an asymmetric fashion. The axons run anteriorly and medially; some of them cross the midline in the cerebellum. Two types of glial cells are impregnated in the cerebellum at E17. First, radial glial cells extend from the ventricle to the pial surface. Secondly some glial cells have lost contact with the ventricle and send several extensions to the pial surface. They correspond to the earliest stage of differentiation of the Golgi epithelial cells and the Bergmann glia (Fig. 3c).

Reeler Embryos. In reeler mutant mice, the tangential growth of the cerebellar cortex is less pronounced than in control animals and no evidence for cortical foliation is found. The Pukinje cells, which, for the first time, are unequivocally identified in Golgi preparations, are located without apparent organization beneath the EGL. Some of them attain a normal position and assume a normal orientation. A large proportion of them, however, settle in heterotopic positions in the depth of the cerebellum. They are maloriented or inverted and develop a distorted dendritic tree. The axon leaves the cell from its external, lateral or internal face. After a variable initial pathway, it regains its normal trajectory (Fig. 3d). In parallel to the growth of the cortex, the transversal spreading of the roof nuclei and their subdivision into medial, intermediate and lateral components occur normally in reeler mutants. The dendritic and axonal arborizations of neurons in the central nuclei are comparable to their normal counterparts. The EGL and the glial cells appear similar in both genotypes.

The Cerebellum in the Newborn (Fig. 4)

a) Central Nuclei (Fig. 4). At birth, the central nuclei and their divisions are well visible. The medial nucleus is located medially and has a rounded shape. In reeler mutants, it is slightly displaced externally because of the condensation of heterotopic Purkinje cells near the raphe ("central Purkinje cell mass" of Mariani et al. 1977). The lateral nucleus is found in the depths of the hemisphere. In the normal animal, it has the form of a "U", open medially, with a dorsal and a ventral branch. The opening of the "U" corresponds to the hilus of the nucleus. In the mutant, we were unable to define any organization in the lateral nucleus. The "U", the hilus and the two branches are not clearly visible. In both genotypes, the intermediate nucleus is located between the medial and lateral nuclei; its borders are poorly defined. It should be pointed out that demarcation of the cerebellar nuclei, particularly the lateral and intermediate, is more difficult in reeler than in normal mice. This is because sometimes there is no clear distinction between heterotopic Purkinje cells and neurons of central nuclei, and a partial mixing of the two populations occurs at the periphery of the nuclei.

b) The Cerebellar Cortex. Normally, four folia are present at birth, and two features already noted at E17 appear to be very characteristic of the foliation process. First, the fissures are better perceivable at the level of the Purkinje cell layer, in the depths of the cortex. Second, the topography of the indentations coincides with the presence of radially penetrating vessels. In the mutant animal, no foliation is noted. Despite the concomitant reduction of the cerebellar surface, the thickness and cell density of the external granular layer are normal. Purkinje cells are found at every level, from the roof nuclei to their normal position. They are loosely arranged and, instead of forming a thin layer as in the normal animal, they tend to form poorly defined masses. The most important of these Purkinje cell masses is the central Purkinje cell mass, located near the raphe. The other Purkinje cells form two loose masses, one in the center of the hemisphere, between the lateral nucleus and the surface, the other between the lateral and medial nuclei.

Discussion

The embryonic development of the mammalian cerebellum has been studied in mice (Tello 1940), in the rat (Korneliussen 1968; Altman and Bayer 1978), in cetacea (Korneliussen 1967), in the rhesus monkey (Rakic 1971) and in Man (Rakic and Sidman 1970); Zecevic and Rakic 1976). Autoradiographic studies, especially determination of neuronal "birthdates", were performed in mice (Uzman 1960; Miale and Sidman 1961; Sidman 1970), in the rat (Altman and Bayer 1978) and in the monkey (Rakic 1971; Gould and Rakic 1981). The vast majority of these studies deal mainly with the development of the cerebellar cortex. The issue of the prenatal development of the central nuclei was studied in pig embryos by Dowd (1929) and more recently in the rat (Korneliussen 1968). In the present work, the embryonic development of the cerebellum is examined comparatively in normal and reeler mice. The observations reveal certain features of cerebellar histogenesis which, to our knowledge, have not been extensively considered hitherto.

1. The Development of the Central Cerebellar Nuclei

In both genotypes, the neurons destined for the roof nuclei migrate at the rostromedial level of the cerebellar bud where they condense into a rounded mass, well defined at E14. At later stages, and in parallel to the tangential growth of the cortex, the nuclei become buried in the depths of the cerebellum and spread out in the transversal plane. The subdivision into medial, intermediate and lateral components is first seen at E17 and is well-defined at birth. Although the sequence of maturation appears to be similar in both genotypes, some differences between normal and reeler animals, from E17 onward, are observed (Fig. 5). First, due to the presence of abundant Purkinje cells near the raphe, the mutant medial nucleus is slightly displaced outwardly. Second, the lateral cerebellar nucleus in reeler mutant mice apparently does not assume its normal shape, and its hilus is poorly defined.

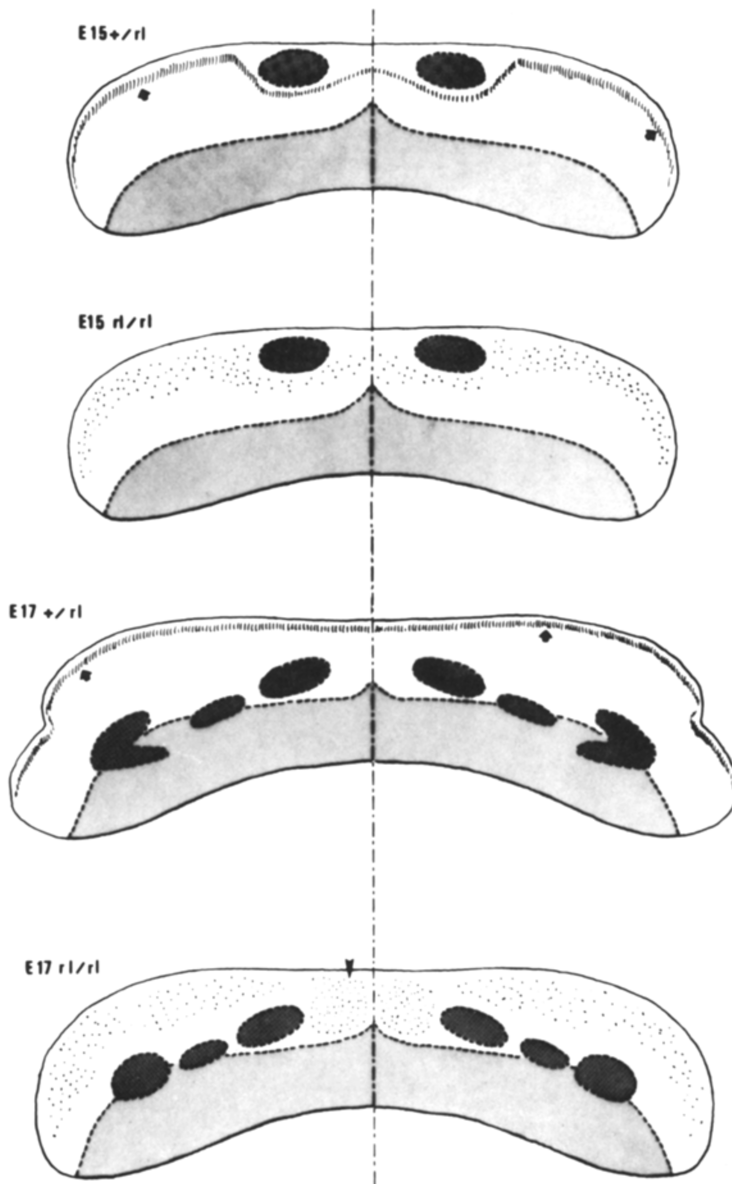

Fig. 5. Schematization of cerebellar development at the early stage (E15) and at late embryonic stage (E17). The normal Purkinje plate is represented as small vertical bars (*arrows*). The mutant Purkinje cells are shown as *dots;* an *arrowhead* points to the central Purkinje cell mass. The central cerebellar nuclei (*dark gray*) form three components at E17. In reeler mutants, the lateral nucleus is not foliated. The ventricular zones are schematized in *light gray*

The existence of some abnormalities of the lateral cerebellar nucleus in reeler mice has been mentioned previously by Caviness and Sidman (1972). The abnormal cytoarchitectonic development of the central cerebellar nuclei in reeler mutants might reflect a primary action of the mutant gene on several targets. The possibility that this abnormality is related to the malformation of the cerebellar cortex cannot be excluded.

2. The Development of the Cerebellar Cortex

At the end of their migration, the normal Purkinje cells assume a radial differentiation and are condensed in the purkinje plate. The PP is bracketed between the MZ and the fiber-rich subPP. In reeler mutants, the Purkinje cells fail to arrange themselves into a plate and this defect ultimately leads to a poorly foliated cerebellum. As quoted by Caviness and Rakic (1978), the initial radial orientation of Purkinje cells appears necessary for the formation of a normally convoluted cerebellar cortex. Obviously, this necessary condition is not sufficient. The presence of a normal population of granule cells (in terms of proliferation and migration), is necessary for foliation to proceed beyond three to four folia, as shown in the work of Haddara and Nooreddin (1966), as well as by the observations on weaver and staggerer mutant mice (review by Caviness and Rakic 1978). Other unrecognized factors are presumably involved in the foliation process. Foliation clearly begins in the depths of the cortex, at the level of Purkinje cells, and thus cannot be exclusively attributed to constraints acting in the external field of the cortex (i.e. pia, EGL, MZ). Cortical fissures always form at the level of radially penetrating vascular arches. The radial vessels are present well before the initiation of foliation, and could consequently condition the topography of certain cortical fissures. A role for mesodermal structures in the development of cerebellar foliation is suggested from the work of Sievers et al. (1981).

Despite a reduction in the surface of the mutant cerebellum (from E17 onward), the external granular layer has a normal morphology and thickness in reeler mutant embryos, and granule cells are thus diminished in number. This confirms that the proliferation of external granule cells is not primarily regulated by an intrinsic, "internal clock" mechanism (Sensenbrenner 1980), but is dependent on the microenvironment. The EGL spreads on the cortex in close topological relationship with the Purkinje cells, which could provide one of the regulating elements. This possibility has been proposed by Mallet et al. (1976) on the basis of complementary observations.

3. The Cerebellar Malformation and the Action of the Reeler Gene

The present observations are an additional example of the widespread action of the reeler gene. So far, it has been shown that the reeler mutation affects the development of many different structures, like the cerebral cortex (Pinto-Lord and Caviness 1979), hippocampus (Stanfield et al. 1979), olfactory bulb (Wyss 1980), cochlear nuclei (Martin 1981), inferior olivary complex (Goffinet 1983), tectum and lateral geniculate nuclei (Frost et al. 1982) and

the nucleus of the facial nerve (Goffinet 1983). These structures apparently have nothing in common. They are affected to variable degrees, sometimes very mildly (olfactory bulb, facial nucleus). It appears probable that developmental defects will be demonstrated elsewhere, and that the reeler gene may affect all cells in the nervous system. In all cases where detailed examination has been undertaken (especially with regard to embryogenesis), the neurons in reeler mutants appear to be generated at the normal time (Sidman 1970; Caviness 1982), to migrate in the right direction and to assume a good degree of differentiation (judging from Golgi impregnations and electron microscopy). The common lesion is an abnormal topography of cells relative to homologous elements and to fiber strata. In addition, the malformation is quite moderate at an early developmental stage – e.g. at the level of the cerebellum, at E14 – but becomes increasingly manifest as histogenesis and maturation proceed, at times ending in very distorted neuronal geometry (e.g. pyramidal cells in neocortex). These observations suggest that early architectonic organization of postmigratory neurons is necessary in order for subsequent development to proceed normally. In reeler mutants, the organization of postmigratory cells is defective and the various constraints of maturation could lead to progressively abnormal cytoarchitectonics, while leaving other parameters of differentiation relatively unaffected. In addition to the present results, other observations on cerebellar development are relevant to this hypothesis. First, in reeler-normal (rl/rl – +/+) allophenic mice (Mullen 1977), some areas of the cerebellum express the reeler phenotype. Areas of the cerebellum of both phenotypes contain Purkinje cells belonging to the two genotypes (normal and reeler). Second, when rat cerebellar primordia are implanted in a heterotopic position, the development of cerebellar cortical lamination can proceed quite normally (Kromer et al. 1979; Alvarado-Mallart and Sotelo 1982). Also the formation of a reasonably well-formed cerebellar cortex has occasionally been observed in human teratomas (Willis 1971). These observations show that the development of the normal or reeler phenotype of Purkinje cells is to a large extent independent of a diffusible factor, and that most of the necessary information is intrinsic to the cerebellar neuroepithelium. It is tempting to suggest that the early architectonic organization of postmigratory neurons might occur via interactions between early neurons or between neurons and radial neuroepithelial cells, and that some of these interactions might be abnormal in reeler mutants (Pinto-Lord et al. 1982; Goffinet 1979).

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