The prenatal development of the mammalian cerebral cortex, including that of humans, is characterized by two sequential and interrelated periods: an early embryonic and a late fetal one. The embryonic period is characterized by the establishment of a primordial cortical organization, which is common to all mammals and shares features with the primitive (primordial) cortex of amphibians and reptiles (Marín-Padilla 1971, 1978, 1983, 1992, 1998). Its establishment represents a prerequisite for the subsequent formation, development, and organization of the pyramidal cell plate (PCP), (cortical plate (CP) in current nomenclature), which represents a mammalian innovation. The original description of the dual origin and composition of the mammalian neocortex has been corroborated and, today, is universally accepted. The mammalian fetal period is characterized by the sequential, ascending, and stratified organization of the PCP, which represents the most distinguishing feature of the mammalian cerebral cortex. The term pyramidal cell plate (PCP), used in the present monograph, replaces the current unspecific term of cortical plate (CP) for various reasons. The early PCP is composed solely of pyramidal neurons and represents the mammalian neocortex’s most distinguishing feature (Chapters 3 and 4). Other neuronal elements are incorporated into the PCP later in prenatal development (Chapter 6). The progressive ascending and stratified anatomical and functional maturations of the PCP from lower (older) to upper (younger) pyramidal neurons are concomitant with the ascending and also stratified incorporation and maturation of its associated fibrillar, synaptic, excitatory-inhibitory, microvascular, and neuroglial systems (Chapters 4, 6–8).

The mammalian neocortex embryonic period starts in the very young embryo, evolves rapidly and represents a transient cortical organization. The establishment, throughout the embryonic cerebrum, of the primordial cortical organization follows a ventral (proximal) to dorsal (distal) gradient that coincides with the advancing penetration of primordial corticipetal fibers and of migrating primordial neurons throughout the cortex subpial region. This period has been studied in hamsters, mice, and cats and human embryos using both the rapid Golgi and routine staining procedures. The ventral (proximal) to dorsal (distal) progression and its basic neuronal and fibrillar composition is similar in all embryos studied and is considered to be essentially analogous in all mammalian species (see Fig. 11.9).

The mammalian cerebral cortex primordial cytoarchitectural organization goes through four sequential stages, which, in order of appearance, are: the undifferentiated neuroepithelium (NE), the marginal zone (MZ), the primordial plexiform (PP), and the PCP appearance. These stages evolve rapidly and sequentially throughout the cerebrum subpial zone in a ventral (proximal) to dorsal (distal) gradient. In whole brain preparations, it is possible to observe the transformations of one stage into the next (Figs. 11.3a and 11.9). This developmental gradient, observable in the four stages, has been crucial for understanding the appearance, chronology, and interrelationships of the cortex early neuronal and fibrillar components. Although, the following descriptions emphasize each embryonic stage essential features, they should be understood as a continuum.

**Neuroepithelium (NE) Stage.** The cerebral cortex original neuroepithelium is composed of closely packed ependymal (ventricular) cells attached to both the ependymal and the pial surfaces. The neuroepithelial cells are closely packed and their bodies are found throughout all levels excepting at the zone
immediately below the pial surface occupied by their terminal filaments (Fig. 2.1a, b). The neuroepithelial cells are attached to the pial surface by filaments with several terminal endfeet, which united by tight junctions, build the pia external glia limiting membrane (EGLM) and manufacture its basal lamina (Fig. 2.1a, b). The pial surface represents the inner (basal) surface of the original neuroectoderm and its basal lamina before its closure and subsequent transformation into a neural tube. These cells are also attached to the ependymal surface. Cells at various stages of mitoses are recognized, in a ventral to dorsal gradient, through the ependymal surface (Fig. 2.1b, arrow heads). These mitotic cells add new components to the cortex expanding neuroepithelium and, eventually, some of them will participate in the generations of both neuronal and glial cells precursors destined to the cortex developing white and gray matters.

The mammalian neocortex NE stage is recognized in 9-day-old hamster and mouse, 19-day-old cat and 40-day-old human embryos (Fig 3.1a).

**Marginal Zone (MZ) Stage.** The continuing growth and surface expansion of the cortex requires of a sustained incorporation of new radial glial endfeet and additional basal lamina material. The increasing number of radial glial terminal filaments conveys to the subpial zone a light fibrillar appearance known as the MZ (Fig. 2.1a, 20 days). The presence of arriving primordial corticipetal fibers also contributes to its fibrillar appearance. A few scattered neurons, lacking distinctive morphological features, start to be recognized through the developing cortex proximal region (Fig. 2.1a, 20 days). The early primordial neurons and corticipetal fibers arrive at the MZ from extracortical sources, via the CNS subpial region (Zecevic et al. 1999). Some of these early neurons seem to originate in the medial ganglionic eminence. The origin of the early arriving primordial corticipetal fibers remains unknown. It has been suggested that some of them could represent monoaminergic fibers from mesencephalic and/or early thalamic centers; their origin needs to be further investigated (Marín-Padilla and T. Marín-Padilla 1982; Zecevic et al. 1999).

The neocortex MZ stage is recognized in 10-day-old hamster and mouse, 20-day-old cat, and 43-day-old human embryos (Fig. 2.1a, 20 days and see Chapter 3).

**Primordial Plexiform (PP) Stage.** As the number of primordial corticipetal fibers and of neurons increases throughout the subpial zone, it assumes a plexiform appearance (Fig. 2.1a, 22 days, c, d). At this stage, some subpial neurons start to develop specific morphological features. Some neurons, sandwiched among the fibers, assume a horizontal morphology and tend to occupy the subpial upper region, while others assume a stellate morphology and tend to occupy its deeper region (Fig. 2.1c). The early horizontal neurons are recognized as embryonic Cajal–Retzius cells while the deep stellate ones are recognized as pyramidal-like neurons with ascending apical and basal dendrites (Figs. 2.1c, d and 2.2a, b). The embryonic Cajal–Retzius cells are already characterized by horizontal dendrites and axonic terminals distributed throughout the subpial zone upper region (Fig. 2.2). At this time, the deep pyramidal-like cells become the larger neurons of the developing neocortex. These neurons axon branches through the subpial lower region, has ascending collaterals that reach the upper zone, and becomes the source of the early corticofugal fibers leaving the developing cortex (Fig. 2.2a, b). The subpial zone thickness has increased considerably and its fibrillar and neuronal elements have expanded horizontally throughout the cortex (Fig. 2.2a, b). At this age, a thin band of internal white matter composed of both corticopetal and corticofugal fibers start to be recognized through the neocortex proximal or ventral region. In Golgi preparations, some of its fibers have terminal growth-cones advancing in opposite directions suggesting either arriving and/or departing fibers (Fig. 2.2a, b).

At this developmental stage, the mammalian neocortex is considered to be already an early functional system. Because of its appearance and neuronal composition, this early cytoarchitectural and functional organization was originally named the “PP Layer” (Marín-Padilla 1971). It was later renamed the “Prelate.” In mammals, the PP developmental stage is a transient organization recognized in 11-day-old mouse (Fig. 2.1d), 11-day-old hamster (F. 2A), 22-day-old cat (Figs. 2.1c and 2.2b), and in 50-day-old human embryos (Chapter 3).

The PP developmental stage precedes the appearance of the cortex PCP and will regulate its ascending and stratified organization, as well as the ascending placement of its pyramidal neurons from lower (older) to upper (younger) cortical strata.
Pyramidal Cell Plate (PCP) Stage. Migrating neuroblasts, of ependymal origin, start to arrive at the developing neocortex and begin to accumulate precisely within the PP forming a compact cellular plate that eventually extends throughout the entire cortex. This cellular plate, which represents a distinguishing mammalian feature, is renamed, in this monograph, the PCP (Fig. 2.3a). The new PCP terminology is preferable to the current CP, because during its formation it is essentially composed of pyramidal neurons (Chapter 3). Its appearance also follows a ventral (proximal) to dorsal (distal) gradient, which is recognized in sections of the entire embryo brain (Figs. 11.3a and 11.9). The PCP represents a mammalian innovation and its pyramidal cells are the essential and most distinguishing neuronal type of the cortex. Its appearance divides the original PP neuronal and fibrillar components into elements that remain above it and those that remain below it (Fig. 2.3a, b). Thus establishing simultaneously the cortex first lamina (I) above it and the subplate (SP) zone below it (Fig. 2.3a, b). All PCP pyramidal neurons originate intracortically from mitotic cells within the ependymal epithelium. The pyramidal cell original precursors, using radial glia filaments as guides and attracted by
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reelin from Cajal–Retzius cells, ascend up to the PP zone and accumulate progressively within it (Rakic 1972, 1988; Marín-Padilla 1992). The newly arrived neuroblasts after losing their glial attachment are transformed into mammalian pyramidal neurons with an apical dendrite that branches within the first lamina forming a bouquet, establish functional contacts with Cajal–Retzius cells, and develop a rudimentary descending axonic process (Fig. 2.3); see also Chapters 3–5.

At this stage, the following strata are recognized in the mammalian cortex: (a) a first lamina with Cajal–Retzius cells with horizontal dendrites and axonic processes, the primordial corticipetal fibers horizontal axon terminals, the apical dendritic bouquets of newly arrived pyramidal neurons, the axon terminals of SP Martinotti cells, and the apical dendritic bouquets of SP pyramidal-like neurons (Fig. 2.3a, b); (b) an intermediate PCP stratum composed of immature pyramidal neurons attached to the first lamina by their apical dendrites (Fig. 2.3a, b); (c) a deep SP zone stratum with large pyramidal-like neurons with ascending apical dendrites that reach and branch within the first lamina, with several basal dendrites and an axon that after giving off several collaterals penetrates into the internal white matter and becomes a corticofugal fiber; (d) a thin internal white matter composed of both corticipetal and corticofugal fibers (Fig. 2.3a, b); (e) a thick matrix zone composed of closely packed cells; and (f) an ependymal epithelium with numerous mitotic cells and the attachment of numerous radial glial cells. The SP pyramidal-like neurons axon has ascending collaterals that reach the first lamina and several horizontal collaterals distributed through the zone (Fig. 2.3b). The SP zone has also Martinotti neurons with basal dendrites and an ascending axon that reaches and branches within first lamina (Fig. 2.3b).
Some of the white matter fibers depict growth-cones advancing in opposite directions, suggesting the presence of both corticipetal and corticofugal fibers (Fig. 2.3b). At this age, the cat motor cortex PCP consists of a compact cellular plate (3–5 cells thick) composed of pyramidal neurons with smooth (spineless) apical dendrites that branch into the first lamina with short descending axons. The PCP advancing formation, from proximal (ventral) to distal (dorsal) cortical regions, delineates the simultaneous and sequential establishment of the neocortex first lamina and SP zone (Fig. 2.3a). At this age, the cat embryonic cortex distal region still is at its PP developmental stage (Fig. 2.3a). At this age, the matrix, the proximal paraventricular zones and the striatum has started to develop their intrinsic microvascular system (Fig. 2.3a). Also, at this age, most the embryonic cortex is still avascular but covered by a rich pial capillary anastomotic plexus that extends throughout its entire surface (Fig. 2.3a).

In the original descriptions, the cytoarchitecture composition of the cat cortex PP and early PCP were considered to share features with the amphibian and reptilian primitive cortices (Marín-Padilla 1971, 1978, 1992, 1998). As in reptiles, the embryonic mammalian cortex basic functional elements include Cajal–Retzius neurons on its outer zone, pyramidal-like projective neurons and Martinotti cells on its inner zone, and an internal white matter with both corticipetal and corticofugal fibers. At this age, the few pyramidal neurons of the PCP are considered to be undifferentiated and functionless with descending axons that barely reach the internal white matter.

The fact that the early cytoarchitectural organization of the embryonic mammalian neocortex should resemble that of phylogenetically older species is not surprising since it reflects a continuous process that interconnect the evolution of these three vertebrates (Marín-Padilla 1971, 1972, 1978, 1992, 1998). This developmental conception led to hypothesize the dual origin and composition of the mammalian cerebral cortex (Marín-Padilla 1971, 1978). Consequently, the first lamina and SP zone of the mammalian neocortex represent elements of a primordial cortical organization that shared features with the primitive cortex of amphibian and reptiles. To this primordial cortical organization, a PCP, which represents a mammalian
innovation, is progressively incorporated. The newly formed PCP up to around the 15-week-of gestation is composed essentially of undifferentiated pyramidal neurons anchored to the first lamina by their apical dendrites and smooth somata with short descending axons. Eventually these pyramidal neurons become the major component of the cortical gray matter (Chapters 3 and 4). Consequently, the term “neocortex” often used to describe the mammalian cerebral cortex seems most appropriate.

These four early embryonic stages evolve rapidly (in days) and throughout a still avascular neocortex. As a neuroectodermal tissue, the early cortex is deprived of an intrinsic microvascular system and, eventually, will have to develop one. The embryonic cerebral cortex is surrounded by well-vascularized meninges (Chapter 7). The pial anastomotic capillary plexus evolves from meningeal arachnoidal vessels and progressively covers the entire cortex surface, the primordial hippocampus, and supplies the choroid plexus vasculature. This rich anastomotic pial capillary plexus covers the neocortex surface through its early (NE, MZ, PP and early PCP) embryonic stages. These pial capillaries are separated from the cortical elements, only by the pial EGLM and its basal lamina. Undoubtedly, the close proximity of these capillaries to the cortex early neuronal and fibrillar elements allows sufficient oxygen diffusion to guarantee their early evolution. Eventually, capillary sprouts from this plexus will perforate through the neocortex basal lamina and the EGLM and penetrate into the nervous tissue, progressively establishing the various compartments of the cerebral cortex extrinsic and intrinsic microvascular systems (Chapter 7).

References

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