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Invited Review

Transient structures of the human fetal brain: Subplate, thalamic reticular complex, ganglionic eminence

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Summary. Morphological features of the subplate, the thalamic reticular complex and the ganglionic eminence, which represent three major transient structures of the human fetal forebrain, are summarized with special reference to their functional roles. The subplate harboring various neuronal types is an outstandingly wide zone subjacent to the cortical plate in the human fetal brain. Within the subplate various cortical afferents establish synaptic contacts for a prolonged period before entering the cortical plate. Therefore, the subplate is regarded as a "waiting compartment" which is required for the formation of mature cortical connections. Next to the thalamic reticular nucleus, within the fibers of internal capsule, the perireticular nucleus is located which has been established as a distinct entity during development. Its various neuronal types express a number of different neuroactive substances. Perinatally, the perireticular nucleus is drastically reduced in size. It is involved in the guidance of corticofugal and thalamocortical fibers. The ganglionic eminence is a conspicuous proliferative area that persists throughout nearly the entire fetal period. In the human fetal brain it extends medially upon the dorsal thalamic nuclei which receive precursor cells from the ganglionic eminence. Postmitotic cells in the marginal zone of the ganglionic eminence serve as an intermediate target for growing axons. On the whole, all three structures establish transient neural circuitries that may be essential for the formation of adult projections. The characteristics of the three transient structures are particularly relevant for developmental neuropathology as these structures may be damaged in disorders that preferentially occur in preterm infants.

Key words: Migration, Axonal pathfinding, Arnygdala, Gangliothalamic body, Perireticular nucleus

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Abbreviations:

TRH: pro-a-thyrotropin-releasing hormone; A: amygdala; AB: accessory basal nucleus of the amygdala; Ac: nucleus accumbens; AChE: acetylcholinesterase; B: basal nucleus of the amygdala; C: nucleus caudatus; CA: anterior commissure; CB: calbindin; Ci: internal capsule; CE: central nucleus of the amygdala; Cl: claustrum; CP: cortical plate; CR: calretinin; E: embryonic day; EC: entorhinal cortex; ECM: extracellular matrix; GABA: gamma-aminobutyric acid; GAP-43: growth-associated protein; GP: globus pallidus; GTh: gangliothalamic body; ICH: intracranial hemorrhage; IL-6: interleukin-6; ir: immunoreactive; IZ: intermediate zone; L: lateral nucleus of the amygdala; MAP2: microtubule-associated protein 2; NCAM: nerval cell adhesion molecule; NPY: neuropeptide Y; P: postnatal day; Pu: putamen; PCNA: proliferating cell nuclear antigen; PAC: periamygdaloid cortex; PR: perireticular nucleus; PV: parvalbumin; PVL: periventricular leukomalacia; R: thalarnic reticular nucleus; Ru: nucleus ruber; SP: subplate; SRIF: somatostatin; STh: subthalamic nucleus; Th: thalamus; TO: tractus opticus; WM: white matter.

Introduction

The histological structure of the immature brain differs from that of the mature one to a considerable extent. The human fetal forebrain displays a number of prominent structures which are transient in nature. Thus, the architectonic organization of the fetal forebrain is distinctly different from that of the adult. This review focuses on three major architectonic structures of the fetal brain: subplate, thalamic reticular complex and ganglionic eminence (Fig. 1). These three transient structures are described with special regard to I) their genesis, II) their architectonic organization, III) their constituent cell types, IV) their neurochemical characteristics, V) their connectivities, VI) their functional roles in development, VII) their resolution, and VIII) their significance in developmental

neuropathology.

Subplate zone

Origin and stages of development

The first cortical neurons generated in the ventricular zone form a single layer called "primitive plexiform layer" or "preplate". Then neurons destined for the cortical plate (CP) migrate through the lower half of the preplate. An increasing number of neurons settling in the middle of the preplate divides the latter into two layers: The outer layer becomes the marginal zone (lamina I), the deeper forms the subplate (SP). Both have been shown to play important organizing roles for the development of the cerebral cortex (Marin-Padilla, 1998). The neurons derived from the preplate are characterized by a precocious morphological and neurochemical differentiation.

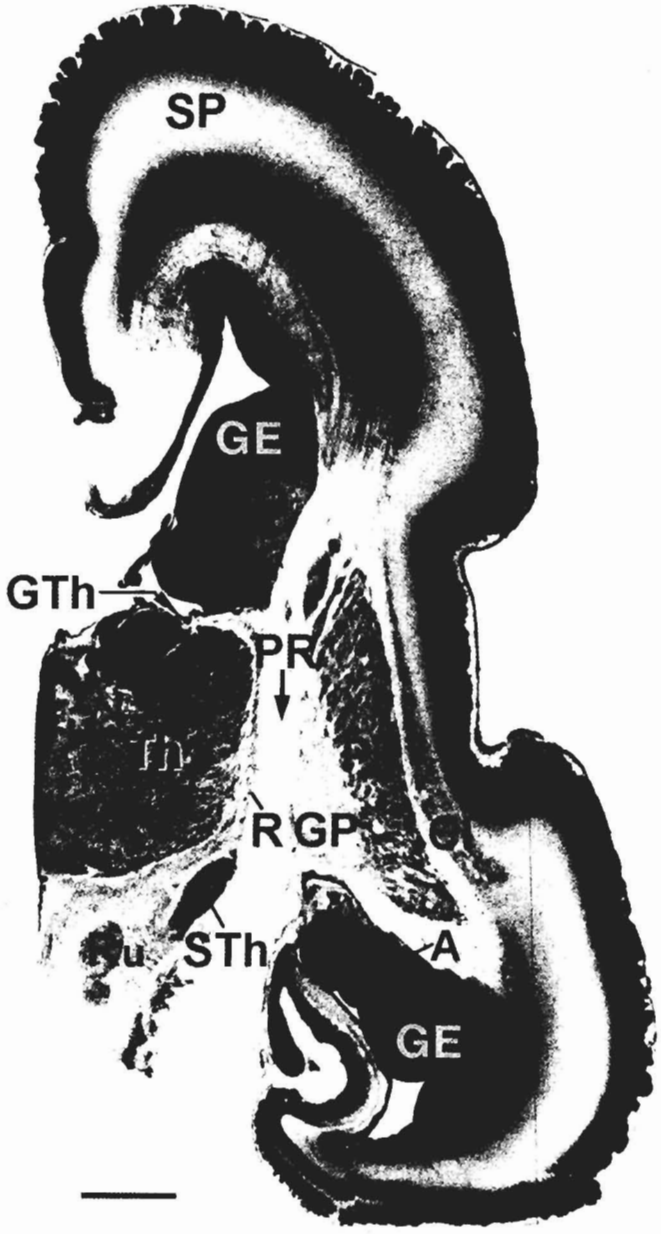


Fig. 1. Frontal section, 100 μm thick, taken from a celloidin-embedded human brain of the 5th gestational month, stained with the Nissl dye Darrow red. Three major transient structures are found in this section: the subplate (SP), the ganglionic eminence (GE) and the perireticular nucleus (PR). For further abbreviations, see list of abbreviations. Scale bar: 2 mm.

Around the 12th gestational week the cerebral wall consists of the ventricular zone, subventricular zone, intermediate zone, pre-SP, CP and marginal zone; the pre-SP being located between the CP and the intermediate zone, is the forerunner of the SP proper. It represents a narrow band-like zone containing distinctly fewer cells than the adjacent cell-dense CP. The latter gives rise to the laminae II-VI which are formed in an ordely sequence (Bayer and Altman, 1991). Deep neurons originate earlier than superficial nerve cells close to laminae I (inside-out-gradient in neocortical neurogenesis). The neurons generated in the proliferative zones and destined to form the laminae II–VI must traverse the SP-zone to arrive within the CP.

Kostović and Rakić (1990) distinguished five stages in the development of the SP: I) pre-SP stage, II) SP formation stage, III) SP stage, IV) SP dissolution stage and V) post-SP stage. I.: The forerunner of the SP is a thin band containing numerous dendritic and axonal processes and polymorphic neurons. The latter display characteristics indicative of a high level of differentiation. The fibers are, in contrast to the CP and intermediate zone, randomly oriented. II.: During this period the SP can be divided into an upper and a lower part. The upper part contains neurons in distinctly higher packing density than the lower part. The latter reveals a fibrillar organization. The upper part gradually increases in width so that a homogeneously even distribution of neurons is observed at the beginning of the next stage. During the SP formation stage SP neurons originate from at least two different locations. The neurons of the pre-SP (I) contribute to the neuronal population of the SP. The majority of SP neurons are likely to be derived from the CP of the pre-SP stage. Neurons originating from the CP are thought to form the upper part of the SP. III.: Two phases can be distinguished within this stage. First, an extensive increase in thickness of the SP is observed (till 22 weeks). Thereafter, the width of the SP remains constant. During the first phase the amount of fibers dramatically increases and all the neuronal types characteristic of the SP occur (see below). During the stationary phase the SP represents the thickest stratum of the cerebral wall. Differences in thickness as seen when comparing various cortical areas are mainly due to differences in the amount of fibers that accumulate in the SP. IV.: During this prolonged period the SP gradually diminishes. Growth cones frequently observed in the SP during the earlier stages become rare. Axons are radially oriented or run in parallel to the pial surface forming thin fascicles. The extracellular space, being a prominent

constituent of the SP in earlier stages, is now drastically reduced. To determine the exact time when the post-SP stage (V) begins appears arbitrary as some SP neurons persist as interstitial white matter (WM) neurons into adulthood.

Nerve cell types

The SP-nerve cells represent a heterogeneous neuronal population with regard to their morphology and their expression of neuroactive substances. In Golgi-preparations four neuronal types have been distinguished according to Mrzljak et al. (1988) and Kostović and Rakić (1990): a. Polymorphic neurons: Between the 13th and 15th week of gestation polymorphic nerve cells represent the predominant neuronal type and are particularly frequent in the upper part of the SP. The somata of polymorphic cells reveal various shapes; their dendrites, displaying variable bifurcation patterns, originate from random sites of the somata. No preferential orientation of these cells is observed. In addition to polymorphic nerve cells, horizontally oriented bipolar and unipolar neurons are frequently observed at the interface of the CP and the SP between the 13th and 15th week; b. Fusiform neurons. From the 17th week fusiform neurons can be seen which have a spindle-shaped cell body. From the latter, which can be oriented in all directions, two long and thick main dendrites emerge which can be extremely long. The axons, usually originating from the main dendrites, are observed to ascend (towards the CP) or descend (towards the intermediate zone); c. Pyramidal neurons. This neuronal type is also discernible from the 17th week. Around 80% of the SP pyramidal neurons display an entirely inverted cell body so that the apical dendrites run towards the intermediate zone and the axons originating at the inverted base or from one of the basal dendrites run towards the CP (inverted SP pyramidal neurons). The SP pyramidal neurons send their axons towards the intermediate zone. Their cell bodies are small and their apical and basal dendrites reveal less branches than those of the large pyramidal cells in the CP; and d. Multipolar non-pyramidal neurons. The multipolar neurons occurring around the 22nd week possess spherical or ovoid somata and stellate dendritic trees emerging from three to five stem dendrites. Their axons may ascend or descend or may run horizontally.

All neuronal types of the subplate appear equally frequent at the various depths of the SP. As a whole the SP neurons reveal a relatively large dendritic surface which facilitates their engagement in various fetal circuitries. The neuronal types of the SP as described above can be clearly distinguished from young neurons migrating through the SP. The latter reveal a small soma size and a bipolar form and are perpendicularly oriented.

Neurochemical characteristics

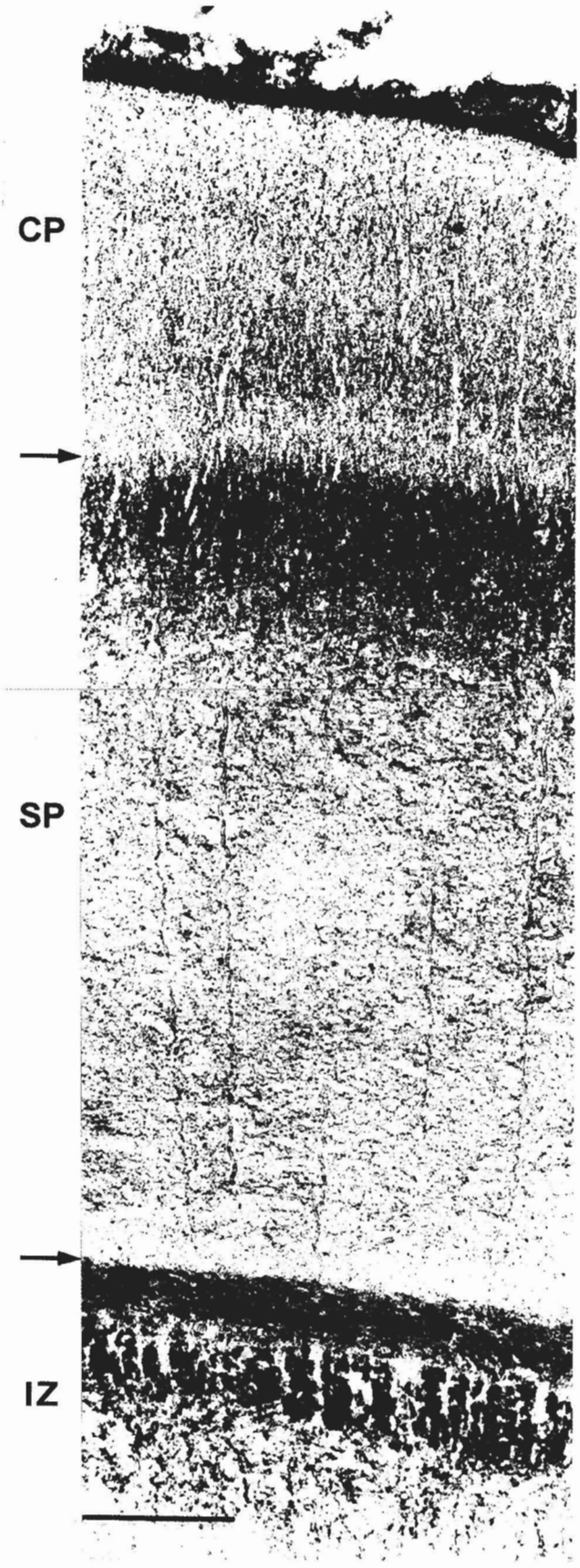
The SP neurons are immunoreactive for GABA (monkey, Huntley et al., 1988; Meinecke and Rakić, 1992), neuropeptide Y (NPY) (monkey, Huntley et al., 1988; Mehra and Hendrickson, 1993), microtubule-associated protein 2 (MAP2) (man, Sims et al., 1988), somatostatin (SRIF) (man, Kostović et al., 1991), substance P (monkey, Mehra and Hendrickson, 1993) and cholecystokinin (cat, Chun and Shatz, 1989). Neurons immunostained by the various antibodies are not evenly distributed within SP-zone. For instance, SRIF-immunopositive nerve cells are mainly encountered within the upper part of the SP, whereas NPY-positive neurons are mostly located in the deeper portion. Moreover, the time frames for the expression of the various substances are to some extent variable. It is conceivable that the different neuronal populations characterized by the expression of different neuroactive substances may interact with different sets of waiting axons (see below). The distribution and density of peptidergic nerve cells undergo considerable reorganization during development. The laminar redistribution may reflect laminar shifts of afferent systems, transient expression of peptides or death of neurons (Kostović et al., 1991).

Furthermore, calcium-binding proteins are found within the SP, i.e. parvalbumin (PV) and calbindin (CB) (rat, Liu and Graybiel, 1992; Enderlin et al., 1987; man, personal observations). The expression of PV is only moderate within the SP; it is restricted to the upper part and occurs rather late in human fetal development (man, Honig et al., 1996). Calretinin (CR) and CB are abundantly expressed within the SP (rat, Enderlin et al., 1987; Fonseca et al., 1995) so that the antibodies directed against these two calcium binding proteins have been suggested to be adequate markers of SP-zone.

In particular, using anti-CR the SP neurons are intensely immunolabelled in the human fetal brain (Fig. 2). In these immunopreparations the borders towards the cortical anlage and the intermediate zone can be well defined. Defining the exact borders of the SP-zone has been a matter of discussion in the literature. It has been suggested that definite borderlines can be accurately drawn only with the aid of H^3-thymidine (Chun and Shatz, 1989). As such an approach is impossible when investigating human specimens it remains to be proven that anti-CR can serve as a reliable marker of the SP-zone at various developmental stages.

Synapses and extracellular matrix

The SP is particularly pronounced in width in the human fetal brain. The constituent fibers and cells of this sizeable transient structure display considerable changes during the course of fetal development. Early arriving axons, such as monoaminergic and cholinergic fibers, may cause an initial dispersion of the cells that form the pre-SP (Schlumpf et al., 1980; Specht et al., 1981; Kordower and Rakić, 1990). Electron microscopic studies (Kostovic and Rakić, 1990) have demonstrated a high number of synapses and an enlarged extracellular



space. Light microscope findings are in accordance with these ultrastructural features. The presence of synapsin I (Chun and Shatz, 1988a) which participates in presynaptic transmitter release indicates that the SP neurons receive synaptic input. Intracellular microelectrode and current source density recordings have shown that the SP-synapses seen in electron microscopy are capable of functional synaptic transmission (Friauf et al., 1990; Friauf and Shatz, 1991).

The extracellular space of the SP displays fibronectin-immunolabelling which decreases after experimental elimination of SP neurons or their developmental disappearance (Chun and Shatz, 1988b). Moreover, chondroitin-sulfate proteoglycans are enriched in the SP (Bicknese et al., 1994). Emerling and Lander (1996) demonstrated that dissociated embryonic thalamic neurons extend their axons into the SP only when chondroitin-sulfate is present within this zone. In addition, laminin (Hunter et al., 1992) and the adhesion molecules L1 and neural cell adhesion molecule (NCAM) are expressed in the SP (Godfraind et al., 1988; Chung et al., 1991). Some of the extracellular matrix (ECM) and adhesion molecules are only expressed in the SP, but not in the CP. Thus, they may provide a unique extracellular milieu in the SP that is required for the functions of the SP in axonal growth.

Subplate as a waiting compartment

Several fiber systems reside transiently within the SP-zone. The width of this zone gains considerably in size during fetal development, most probably due to an ingrowth of fibers. The SP-zone harbors axonal plexus of various afferent systems. The axons which establish synaptic contacts with SP neurons stay in the SP for a prolonged period of development prior to entering the CP. Therefore, this zone has been considered as a "waiting compartment". This concept implies the main function of SP neurons which have been demonstrated to mediate the sequential and orderly formation of connections between various subcortical nuclei and the appropriate cortical target areas.

A sequential appearance of different afferent projections in the SP has been described (Kostović and Rakić, 1990). First, i.e. around the 12th gestational week, monoaminergic input coming from brain stem nuclei arrives (Zečević, 1993; Verney et al., 1995). Cholinergic fibers arising in the magnocellular nuclei of the basal forebrain appear to be the second afferent system of the SP (Kostović, 1986). In the occipital lobes an accumulation of cholinergic fibers visualized by acetylcholinesterase (AChE)-histochemistry is observed between the 15th and 18th week (Kostović and Rakić,

Fig. 2. Calretinin-immunopreparation of the occipital lobe, 100 μm thick, 25th gestational week. Due to differential immunolabelling patterns in the subplate (SP), cortical plate (CP) and intermediate zone (IZ) the borders between the CP and SP on the one hand and between the SP and IZ on the other can clearly be seen. Both borders are marked by arrows. Scale bar: 500 μm.

1984). The cholinergic fibers reach the SP before the thalamocortical axons. This observation is in accordance with the finding that the cholinergic neurons of the basal forebrain exhibit an early maturation in the human fetal brain (Paul and Ulfig, 1998). The next afferent system stems from the dorsal thalamic nuclei. It has been well documented that these thalamic fibers arrive at the appropriate cortical area long before their target neurons in lamina IV have migrated into the CP (Ghosh et al., 1990; Herrmann et al., 1994). After settling of lamina IV neurons thalamic axons grow into the CP to contact their final target neurons. Clear experimental evidence has been provided that after selective destruction of SP neurons thalamic fibers fail to find their appropriate target area. As a result of selective elimination of SP neurons thalamo-cortical fibers fail to enter the cortex at the appropriate site; instead, they grow aimlessly in the subcortical region (Allendoerfer and Shatz, 1994; Molnár and Blakemore, 1995). SP neurons, furthermore, are involved in the interactions leading to the formations of ocular dominance columns in the visual cortex. Thus, SP neurons are required for the refinement of thalamic connections within lamina IV (Ghosh and Shatz, 1992).

The last axons to arrive are those forming ipsi- and contralateral cortico-cortical connections which remain the longest and form a large contingent of fibers in the SP. Differences in the thickness of the SP in various cortical areas are mainly due to the number of cortico-cortical fibers. For instance, the SP of the visual cortex which receives little commissural and associational projections is distinctly smaller than for instance the SP of cortical association areas. In line with this consideration thin SP-zones characterised by a paucity of cortical afferents also undergo early resolution (Kostović and Rakić, 1990).

Involvement in gyral formation

The SP, moreover, may be involved in the formation of cerebral gyri. Experimental studies in which subcortical fiber bundles were surgically interrupted demonstrated that the arrangements and numbers of thalamocortical and cortico-cortical projections are likely to play an important role in the development of gyri (Goldmann-Rakić and Rakić, 1984; Rakić, 1988). The thickness of the SP being predominantly determined by the number of afferent axons is distinctly different in the various cortical areas. The regional differences in SP thickness are in register with the occurrence of sulci and gyri so that the emergence of sulci and gyri is accompanied by the peak of SP-thickness (Kostović et al., 1989; Kostović and Rakić, 1990). Accordingly, species with lissencephalic brains display only very thin SP-zones (Crandall and Caviness, 1984; Van Eden and Uylings, 1985; Jackson et al., 1989). Another observation substantiates a relationship between the SP-zone and cerebral convolutions. Tertiary gyri of the frontal lobe only develop postnatally; in these locations the SP-zone persists for a longer period after birth (Kostović et al., 1989).

Connections of subplate neurons

Many of the synapses found within the SP reveal symmetric membrane junctions (Kostović and Rakić, 1990). GABAergic neurons which are known to form symmetric synapses are found within the SP. Moreover, SP neurons in the developing primate occipital cortex have been shown to express GABA receptors. It is conceivable that these neurons may represent local circuit nerve cells which terminate upon dendrites of other SP neurons, thus influencing physiological response properties and specificity of the transient connections within the SP (Meinecke and Rakić, 1992).

In addition to these transient local circuits the SP contains projection neurons which send their axons as a pioneer pathway towards subcortical targets (McConnell et al., 1989). These pioneer axons may provide a scaffold which guides thalamic axons to the cortex and descending CP projections to their subcortical targets. The establishment of connections comprises two distinctive developmental steps: I) target recognition; and II) target invasion. McConnell et al. (1994) provided evidence that descending SP connections may aid CP neurons to invade their appropriate subcortical target.

The neurons of the SP do not only have local circuitry axons within the SP and descending axons performing pioneer function for corticofugal projections but also send axons into the CP. These axons terminate within the marginal zone and cortical laminae IV (Friauf et al., 1990). So far, it is not known whether a single SP neuron may send both ascending and descending projections. Furthermore, Chun et al. (1987) and Chun and Shatz (1989) demonstrated that SP neurons project to the contralateral hemisphere (Fig. 9). As a whole, the transient patterns of fetal neuronal circuitry may represent a substrate for transient functional and behavioral phenomena. Thus, this connectivity may provide a basis to explain cortical electric responses, transient behavioral states and sleep patterns in preterm infants (Kostović et al., 1995).

Resolution of the subplate

The SP-zone diminishes and finally disappears at a distinctly slow rate. The end of this process of disappearance is difficult to determine as some SP neurons persist and are encountered as interstitial neurons within the adult WM. So far, it is not possible to predict which neuronal types of the SP survive into adulthood. Moreover, the departure of terminals from ipsilateral and contralateral cortical connections marks the resolution of the SP.

One possible mechanism underlying the decrease in neuronal density of the SP neurons could be their dilution in the increasing volume of the WM. Studies using detailed statistical analysis were undertaken to provide data on the effect of growth on nerve cell

dilution (Wood and Zinsmeister, 1991; Wood et al., 1992). It is obvious from these investigations that growth alone cannot account for the reduction in number of SP neurons.

Several lines of evidence strongly support the notion that cell death is the major event in the resolution of the SP. The extent of neuronal death differs between the various cortical areas and among the different neuronal types found in the SP. Various mechanisms involved in survival and death of SP neurons have been postulated. Neurotrophic factors such as nerve growth factor (NGF) or related neurotrophins (Kordower and Mufson, 1992; Allendoerfer and Shatz, 1994) may play a role in the maintenance of SP neurons. Possible sources of NGF may be the targets of SP projections such as thalamus, tectum or SP neurons themselves (via an autocrine mechanism), whereas the CP is not a likely candidate, as it displays only very low levels of NGF at times when the SP is highly developed (Allendoerfer and Shatz, 1994). The disappearance of NGF-receptor-positive neurons is not due to neuronal death as many MAP2-positive SP neurons can still be detected (Allendoerfer et al., 1990). Thus, a down-regulation of NGF-receptor expression in SP neurons can be assumed before a great number of them undergoes cell death. As has been shown for the cholinergic neurons of the basal forebrain NGF might also serve as a factor that sustains SP neurons (Seiler and Schwab, 1984). Thus, the disappearance of NGF-receptor immunoreactivity may mark the beginning of the resolution period in the SP as its neurons can no longer respond to the ligand.

Wolozin et al. (1988) demonstrated that SP neurons are immunostained with the antibody Alz-50 which recognizes a 68-kDa protein that accumulates in neurons from Alzheimer brains. They speculated that SP neurons being Alz-50-immunoreactive (ir) undergo cell death as do those Alz-50 positive neurons in individuals with Down syndrome or Alzheimer disease. So, SP neurons could actively switch on a program of "death genes".

Another mechanism of neuronal death has been discussed in the literature. SP neurons may die due to an excitotoxic event. It has been proposed that glutamate released by waiting axons plays a role (Molnár et al., 1991) during the death period, as SP neurons are suggested to be vulnerable to glutamate neurotoxicity (Choi, 1992; see also Allendoerfer and Shatz, 1994). Taken together, further studies are needed to determine what mechanism(s) mainly contribute to the resolution of the SP.

Interstitial neurons of the adult white matter

The WM of the adult human telencephalon contains large numbers of isolated neurons lying among the myelinated fiber tracts. These nerve cells are referred to as "interstitial neurons" of the adult WM, a term originally used by Ramon y Cajal (1911). The total number of interstitial neurons representing remnants of the SP is commonly underestimated (Meyer et al., 1992). Kostović and Rakić (1990) suggest that this number in the primate brain approaches the number of neurons in the inferior olive, red nucleus, medial and lateral geniculate nucleus combined. In their Golgi-preparations they could differentiate two types of interstitial neurons: I) polymorphic nerve cells, which are mainly found in vicinity to the cerebral cortex; and II) fusiform nerve cells, which are predominantly seen in the depth of the WM.

The thalamic reticular complex

Description and definition

All thalamocortical and corticothalamic axons must traverse the thalamic reticular nucleus (R), a sheet of neurons located on the lateral margin or the dorsal thalamus (Th). This shell-like nucleus lying between the external medullary lamina and the internal capsule (Ci) is composed of GABAergic neurons. The latter provide inhibitory projections to the dorsal thalamic nuclei (Jones 1975, 1985). The thalamocortical and corticothalamic axons passing through the R give collaterals to the R. Moreover, afferents of the R come from the cholinergic magnocellular nuclei of the basal forebrain and various nuclei of the brainstem (Cornwall et al., 1990; Paré et al., 1990). In the adult human brain the R appears inconspicuous as it contains only a low number of nerve cells. The human fetal R, in contrast, is characterized by a high packing density of neurons which makes the R appear as a prominent structure. Another outstanding feature in the fetal brain is the presence of neurons that show a remarkable similarity to R neurons within the Ci. This group of neurons lying among the fibers of the Ci is referred to as the perireticular nucleus (PR). It is mainly located between the R and the globus pallidus (GP). This PR has been established as a distinct entity during development in animal studies (Mitrofanis and Guillery, 1993) and has been demonstrated in man (Ulfig, 1995; Letinić and Kostović, 1996). In two earlier studies the PR has been briefly described as a large nerve cell group within the Ci of the developing rat brain (Marchand and Lajoie, 1986; Marchand et al., 1986). These authors refer to this cell group as the "nucleus of the ansa lenticularis" which exactly corresponds to the PR.

The R is sometimes in continuity with the PR; frequently, both are clearly separated from each other. The constituent neurons of the PR lie simply or in differently shaped clusters of variable size between the fibers of the Ci. PR neurons are found along the entire antero-posterior and supero-inferior axes.

Neuronal types

Various types of nerve cells are seen in the R as well as in the PR (Fig. 3). Bipolar, triangular and multipolar nerve cells revealing considerably variable soma sizes are encountered. Some neurons display a very large

number of the dendrites that occupy a distinctly large area (Ulfig et al., 1998a). Furthermore, one peculiar neuronal type which is characterized by bushy dendritic trees is regularly encountered in the R and PR. A very large number of thin dendrites which arborize at short distances from the soma and often emerge only from one side of the cell body are characteristic of this neuronal type. The elaborated dendritic trees which may interact with growing axons could also be taken as a sign of degeneration. A similar morphological observation

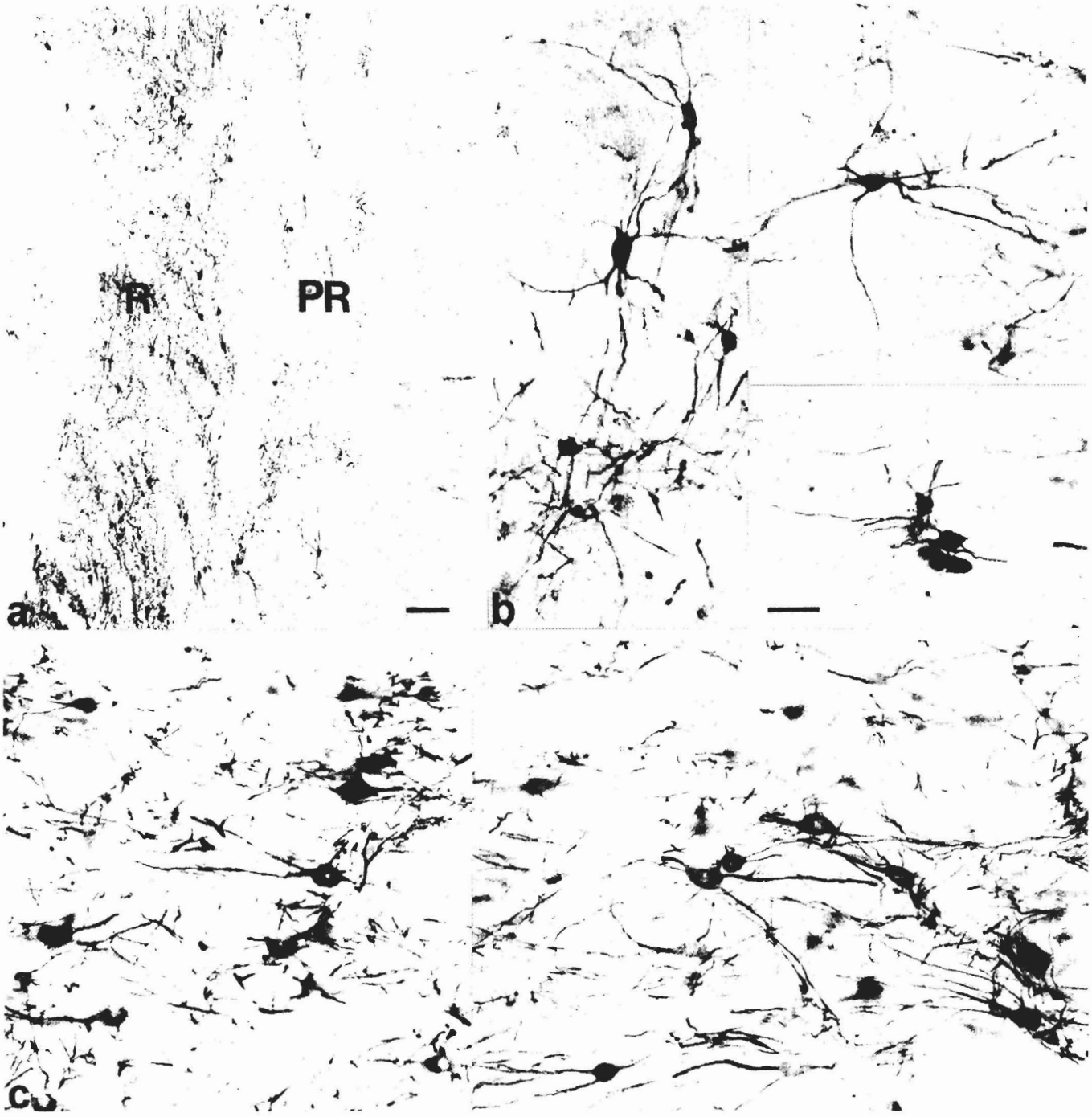


Fig. 3. SMI 311-immunopreparations show the broad band of the reticular nucleus (R) and neurons of the perireticular nucleus (PR) which is located within the internal capsule **(a)**. At the lower part of the microphotograph R and PR are in continuity. Microphotographs of SMI 311 immunoreactive neurons in the PR **(b)** and R **(c)**. The antibody mixture SMI 311, which is directed against non-phosphorylated epitopes of neurofilament proteins, has been shown to immunolabel somata and dendrites in a Golgi-like manner (for details, see Ulfig et al., 1998b). Scale bars: 200 μm (a), 50 μm (b, c).

concerning the dendritic tree has been made for Cajal-Retzius neurons (Meyer and Gonzáles-Hernández, 1993). PR neurons, the bulk of Cajal-Retzius cells and a large number of R neurons are transient cells which undergo cell death.

Apart from the nerve cell type with the bushy dendrites the dendritic trees of the other neurons form a conspicuously dense network within the R. The long dendrites mainly run at right angles to fibers entering or leaving the dorsal Th (Ulfig et al., 1998a).

Neurochemical characteristics

A number of neuroactive substances are expressed in the PR neurons as well as in the R, such as MAP2, somatostatin, SRIF, low-affinity nerve-growth factor (NGF) receptor, the calcium-binding proteins PV, CB and CR, and pro-α-thyrotropin-releasing hormone (αTRH). In addition, they reveal AChE-activity (Mitrofanis, 1992; Letinić and Kostović, 1996; Ulfig et al., 1998a).

The PR neurons have been shown to be among the earliest generated in the Th (Earle and Mitrofanis, 1996). This finding is in line with the outside-in-gradient of neuronal generation and differentiation in the diencephalon. As there is a high degree of resemblance between the PR- and R-neurons both are likely to derive from the diencephalic proliferative zone. Thus, at least a large number of them are generated in the ventricular zone lining the third ventricle. However, it has been postulated that some PR neurons are of telencephalic origin, as the PR is in continuity with the SP during very early development (Mitrofanis, 1994). In the superior part of the human PR of the 6th and 7th gestational month stripes of clustered neurons are seen to directly border upon the margin of the ganglionic eminence. This arrangement of PR neurons suggests that at least some PR neurons originate from the GE during the middle fetal period (Ulfig et al., 1998a). In accordance with this postulation a large number of radial glial fibers providing a scaffold for migrating neurons are detectable in the area where the merging cell clusters are seen at this developmental stage (Ulfig et al., 1999a).

The great majority of R neurons in the human fetal brain coexpress PV and CR (Ulfig et al., 1998a). This finding reflects a transient expression of CR in R neurons, as in the adult only a subset of R neurons, which is restricted to definite areas of the R, is immunostained by anti-CR (Lizier et al., 1997). The bulk of PR neurons also express both CR and PV. Thus, PR neurons appear as outsiders of the R, an observation that has also been described for other species (Mitrofanis, 1992).

Developmental roles

With increasing maturity the PR is distinctly reduced in size, most probably due to nerve cell death. Therefore, it can be assumed that the PR is involved in the regulation of developmental events. Early fibers from the R and PR have reached the dorsal Th before or when thalamic axons are growing out. In the human fetal brain PV-ir fibers probably emerging from the R are among the earliest afferents of the dorsal Th, and they may influence the differentiation of dorsal Th-neurons. Furthermore, the early R-axons may represent pioneer axons that may provide guiding cues for growth cones of outgrowing thalamic axons and, later on, of corticothalamic fibers (Mitrofanis, 1994; Molnár et al., 1998; Ulfig et al., 1998a).

Evidence has been provided that the PR is further involved in guiding axons (for review see Mitrofanis and Guillery, 1993). Growing axons have been shown to change course within the PR which may represent an intermediate target region for elongating corticothalamic and thalamocortical fibers. Fibers coming from the cerebral cortex and reaching the PR within the Ci are either destined to further grow towards the dorsal Th or towards the brain stem. With the aid of DiI (carbocyanine dye) the course of developing thalamocortical and corticothalamic axons could be clearly demonstrated. As these axons reach the PR they sharply turn towards the dorsal Th or cortical SP, respectively. Moreover, these axons display a complex interweaving within the PR and R whereas in the adjacent dorsal Th these axons are straightly oriented. Another group of fibers runs among the PR neurons towards the cerebral peduncle without changing course or displaying any interweaving. This group of fibers belongs to the corticospinal and corticobulbar tracts. The PR neurons may thus be a guidepost where a sorting of the corticofugal fibers takes place. Corticothalamic fibers may thus be separated from corticobulbar and corticospinal fibers (Mitrofanis and Baker, 1993; Mitrofanis, 1994).

In accordance with this putative function an early type of membrane contacts, omega formations which are indicative of endo- or exocytotic events have been described as transient interactions. The latter may be related to axonal guidance or growth within the PR (Ramcharan and Guillery, 1997). After many thalamocortical and corticothalamic axons have already reached their targets a formation of synapses within the PR has been observed (Ramcharan and Guillery, 1997). These authors postulated that synapses might play a role in influencing the developmental course of the axons passing through the PR. However, these findings may also indicate that growing axons temporarily reside within the PR which may, thus, represent an intermediate target (see "Comparison between the perireticular nucleus and the subplate").

Apart from the PR neurons, glial cells could be responsible for guiding axons within the Ci. Glial cells are known to be involved in guiding axons and influencing the course of growing axons (McKeon and Silver, 1995; Faissner and Schachner, 1995). Accumulations of glial cells may physically block axon movement. Extending axons also respond to a variety of

molecules of the ECM which are secreted by glial cells, mainly astrocytes. Moreover, the radial glial scaffold along which neurons climb to their target areas may also help guiding axons. In the developing rat brain, glial cells (radial glia, astrocytes and microglia) appear within the Ci only after sorting of fibers has taken place. Thus, it has been concluded that glial cells do not contribute to the sorting process in the area of the PR. In the PR of developing ferrets the arrangement of the radial scaffold does not show any distinct characteristics which would indicate a role of the radial glia in fiber guidance (Mitrofanis et al., 1997). However, in their study these authors demonstrated a close association between the reticular radial glia and the expression of chondroitin-sulfate in the R. They suggested that radial glial cells express and secrete chondroitin-sulfate into the extracellular space where it is discernible between E20 and E30. During this developmental period thalamocortical and cortico-thalamic fibers pass through the R. Later the expression sharply declines. Preliminary results on the human fetal reticular complex show that chondroitin-sulfate is also expressed during fetal development (Ulfig and Bohl, 1998). In addition to diffuse chondroitin-sulfate immunoreactivity these authors find small immunoreactive cells which are also mentioned by Mitrofanis et al. (1997). So far nothing is known about these small cells. On the whole, further investigations are necessary to determine whether other components of the ECM may be involved in the guidance of growing axons in the reticular complex.

Connections of the perireticular nucleus

The PR does not only project to the dorsal Th but also towards the cerebral cortex (Adams and Baker, 1995). This early transient projection is established before or when the first thalamocortical connections are formed. Thus, it is conceivable that PR neurons may establish a pioneer pathway with the cerebral cortex. Reciprocally, SP neurons send the first corticofugal axons which arrive in the Ci (Allendoerfer and Shatz, 1994). So these initial connections could be part of the transient fetal neuronal circuits (Fig. 9) that may be essential for the formation of the mature connections between the thalamus and the cerebral cortex.

Medial subnucleus and pregeniculate nucleus of the reticular complex

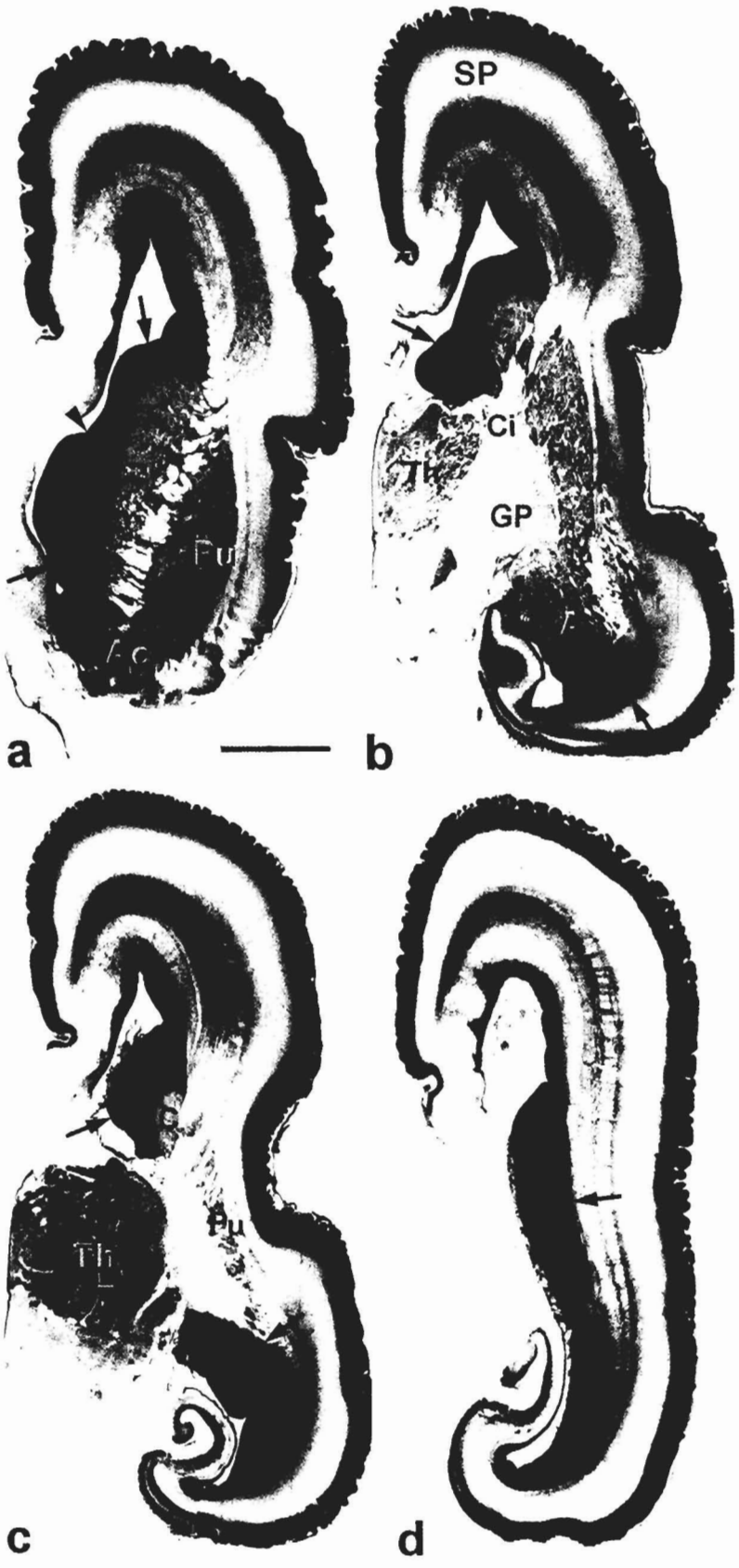
In addition to the main portion (corresponding to the R proper) and the PR two further major constituents of the thalamic reticular complex have been described, i.e. the medial subnucleus and the pregeniculate nucleus (Ulfig et al., 1998a). The medial subnucleus is a band-like structure between the main portion and the dorsal Th and is found in coronal sections through the middle third of the fetal Th. It contains CR-ir neurons, which are all devoid of PV-immunoreactivity. Therefore, this subnucleus stands out clearly in CR-PV-double-immunolabellings. The medial subnucleus, which may well correspond to the inner small-celled region as described by Clemens and Mitrofanis (1992) in cats and ferrets, does not contain GABAergic neurons. It has been regarded as an extension of the zona incerta (Clemens and Mitrofanis, 1992) and it may send projections to the centromedian and parafascicular nuclei of the dorsal Th (Clemence and Mitrofanis, 1992; Royce et al., 1991).

The pregeniculate nucleus, which is in continuity with the inferior part of the PR, lies as a cap-like structure above the superior margin of the lateral geniculate body (Ulfig et al., 1998a). The neurons of this nucleus reveale a moderate packing density and are arranged in two band-like structures lying parallel to the superior surface of the lateral geniculate body. This architectonic component of the reticular complex may also represent a transient target region of growing axons (Mitrofanis, 1994).

Resolution of the perireticular nucleus

A dramatic decline of PR neurons in the rat brain has been shown to occur during a 10-day period (P5-P15) and lead to a disappearance of 98% of the PR neurons (rat, Earle and Mitrofanis, 1996). At P5 the number of PR neurons have reached a peak, and at P15 the number of neurons corresponds to that in the adult. As discussed for the SP, the decrease in neuronal density may be caused via a dilution effect due to growth of the WM. However, with regard to the enormous cell loss, this dilution effect is likely to contribute only slightly to the PR resolution. Evidence has been provided that two other mechanisms underlie the significant PR cell loss: neuronal death and migration of PR nerve cells into the GP. A massive loss of PR neurons is observed during a short perinatal period in rats, largely due to cell death. The latter aspect is reflected by pyknotic profiles found within the PR in the perinatal period (Earle and Mitrofanis, 1996). Comparably, a sharp decline in the density of PR neurons during postnatal development has been described for the human brain (Letinić and Kostović, 1996).

In addition to neuronal death within the PR some PR neurons may migrate into and settle within GP. Within the developing GP neurons are discernible that greatly resemble PR neurons with regard to their morphology and their expression of PV and pro-α-thyrotropin-releasing hormone (Mitrofanis, 1992; Mitrofanis and Baker, 1993). These neurons are no longer visible at around P15 (rat). Experimental data have provided evidence that they most likely undergo cell death within the GP (Earle and Mitrofanis, 1996). In accordance with these data from animal studies groups of PR neurons lying within the lateral portion of the PR merge with neurons of GP and of the medial and lateral medullary laminae (between the segments of the GP and between the lateral segment of the GP and the putamen [P] respectively) in the human fetal brain (Ulfig et al.,



1998a).

Although so far there are only a limited number of observations available in the literature concerning the fate of PR neurons one may assume that there are marked interspecies differences. In the adult Ci of the rat only very few PR neurons can be detected among the fibers. In adult cats and ferrets, however, a distinct PR can be delineated (Clemence and Mitrofanis, 1992). In the adult human brain substantially no PR neurons are present (personal observations). Accordingly, Letinić and Kostović (1996) have shown that only very few PR neurons are present in a 1-year-old infant.

Comparison between the perireticular nucleus and the subplate

There are a number of similarities between the PR and the SP (Earle and Mitrofanis, 1996). 1) Both are generated very early during development; 2) Both consist of neurons lying within future WM. 3) Their neurons, being early differentiated, are morphologically heterogeneous. 4) The SP as well as the PR display complex axonal interweaving. 5) The antigens expressed by both are similar. 6) Both are transient structures being particularly pronounced in the developing human brain. 7) In both areas cell death mainly underlies their reduction in size. 8) As both structures express NGF-receptor the mechanism underlying cell death may involve a loss of trophic support from target cells (or inability to respond to the trophic ligand). 9) Both are involved in the same developmental process: they serve to guide growing axons towards their final targets. 10) Both are suggested to establish pioneer pathways between the cortex and the Th. These transient neuronal circuits may be essential for the formation of adult projections.

Ganglionic eminence

Description

Proliferation of neuronal and glial

Fig. 4. Four frontal sections of 100 μm thickness, Nissl-staining, 5th gestational month, taken from a gapless series of frontal sections. The sections demonstrate the configuration of the ganglionic eminence (GE) marked by arrows. A shallow groove within the GE is visible in **(a)** (marked by an arrowhead); it separates the medial and lateral portion of the GE. The two posterior sections display an already unified GE **(c, d)**. For further abbreviations, see list of abbreviations. Scale bar: 3 mm.

precursor cells takes place in the neuroepithelium lining the ventricles. In particular, during the early and middle fetal period a conspicuous domain is seen within the telencephalic proliferative zone, i.e. the ganglionic eminence (GE). The telencephalic GE represents a prominent bulb-like elevation protruding into the ventricular cavity. Its medial margin directly borders upon the diencephalon (Fig. 5). The GE persists longer than other proliferative areas, and it remains prominent almost throughout the entire fetal period. Mainly precursor cells of the P, the C and the amygdala (A) are generated within the GE. Fig. 6 demonstrates proliferative cells of the GE in high packing density using an antibody against proliferating cell nuclear antigen (PCNA). PCNA is an auxiliary protein that is essential for DNA replication during the S-phase (Hall et al., 1990).

Development of the ganglionic eminence

During early embryonic development (i.e. at the beginning of the second gestational month) a slight thickening in the proliferative zone of the cerebral hemisphere is seen next to the interventricular foramen (Kahle, 1969). Soon after the occurrence of this protrusion a second one is visible. Both elevations are separated from each other by a shallow sulcus. As far as the genesis of these two elevations is concerned, there are many discrepancies between literature reports. Some authors postulated that the groove develops within the initial protrusion with the result that two ridges are then discernible (Tiedemann, 1816). Other authors, however, expressed the view that they are generated sequentially. Humphrey (1968) considered the first elevation to be the future lateral ridge; whereas a number of other authors (Kodama, 1926; Lammers et al., 1980) regarded the first elevation to represent the primordial medial ridge. This latter notion appears most plausible, in particular on the basis of the three-dimensional reconstructions presented by Lammers et al. (1980).

With proceeding development both the medial and lateral GE (ridges) gain in size and, thus, protrusion into ventricles becomes more pronounced. In its vicinity of the primitive foramen of Monro growth of the medial GE gradually causes a narrowing of this foramen. Later, during development, the two ridges unite. Their unification starts in the posterior portion of the GE and proceeds anteriorly. For the human brain a shallow groove separating the medial and lateral GE has been described to occur only in the anterior portion of the GE. Accordingly, in Fig. 4 a shallow groove is visible in the anterior sections of the GE whereas the posterior sections display an already unified GE. In the section located most anteriorly the close relationship between the medial GE and the nucleus accumbens (Ac) is seen. This observation is in line with the assumption that the medial GE represents the site of origin of the human Ac (Kostović, 1990; O'Rahilly and Müller, 1994).

Some authors postulated the existence of three ridges (His, 1904; Ziehen, 1906; Hochstetter, 1919; Kodama, 1926; Källén, 1951). More recent reports, however, did not confirm this observation.

Controversial data exist in the literature concerning the origin of the medial eminence, i.e. whether it is a diencephalic or telencephalic structure. Müller and O'Rahilly (1988, 1989, 1990) proposed to set the boundary between the medial and the lateral eminence. Thus the medial eminence would be diencephalic and the lateral telencephalic. The same authors therefore postulated that some amygdaloid nuclei are derived from the medial eminence; thus the A would - at least in part – be of diencephalic origin. Commonly, however, the GE as a whole is regarded to belong to the telencephalon.

With proceeding development the GE becomes elongated as the cerebral hemisphere gains in size. Associated with the expansion of the cerebral hemisphere in a curved direction to form the temporal lobe the GE develops in a C-shaped manner. As visible in Fig. 4, sections of the middle third of the telencephalon pass twice through the GE which is found laterally in the floor of the central part and in the roof of the inferior horn of the lateral ventricle. According to the C-shaped form the superior and inferior part of the GE are in continuity in sections of the occipital lobe (Fig. 4d). At the end of the pregnancy the GE appears distinctly reduced in size, and only its remnants are visible in Nissl sections (Fig. 5)

In a recent immunocytochemical study the majority

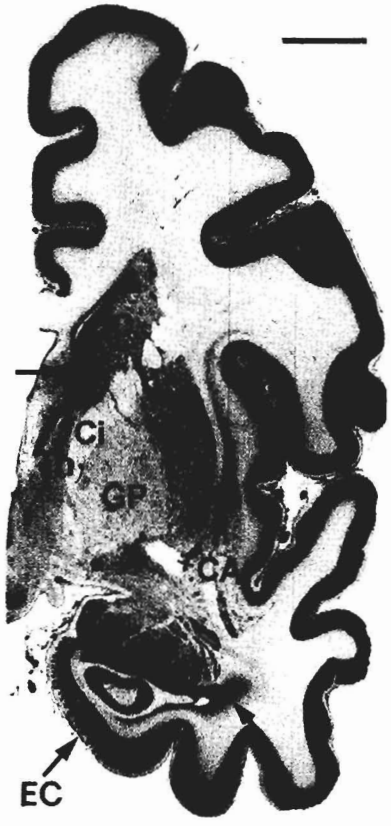


Fig. 5. Frontal section, 100 μm thick, Nissl-staining, 8th gestational month. The remnants of the ganglionic eminece are marked by arrows. For abbreviations, see list. Scale bar: 5 mm.

of GE cells have been shown to express interleukin-6 (IL-6) receptor between the 22nd and 28th gestational week (Ulfig and Friese, 1999). Conspicuously intense immunoreactivity is concentrated in a small rim around the cell nucleus. Immunolabelled cells are found in an extremely high packing density. During late fetal development (i.e. between the 32nd and 36th week) the remnants of the GE contain a moderate number of cells revealing weak IL-6 receptor immunoreactivity.

Characteristics of the interface of the ganglionic eminence and the amygdala

The amygdaloid nuclei which are located in the vicinity of the GE reveal transient architectonic features. In the inferior portions of these nuclei column-like cell-dense areas being separated by cell-sparse septa are visible in Nissl preparations of the 5th gestational month (Fig. 7). These columns, which reveal different widths in the various basolateral amygdaloid nuclei, continuously extend into the GE. In serially adjacent immuno-preparations the columns contain a large number of vimentin-positive fibers (Ulfig et al., 1998d). The latter represent radial glial fibers providing a scaffold for migrating neurons. Thus, the column-like merging areas between the GE and the basolateral amygdala are likely to represent migratory routes. Later on (in the 7th gestational month) neither columns nor merging can be observed. Instead a cell-free stripe separates the GE from the amygdaloid nuclei. This reorganization of the cytoarchitecture is paralleled by rearrangements and final disappearance of radial glial fibers. During the period of decline in radial fibers a transformation of radial glial cells into immature astrocytes takes place (Schmechel and Rakić, 1979; Culican et al., 1990; Ulfig et al., 1998d, 1999a).

Using an antibody directed against growth-associated protein GAP-43 axonal growth, which is reflected by fibrous GAP-43-immunoreactivity can be visualized in the human developing brain (Milosević et al., 1995; Ulfig et al., 1999b). In the 5th and 6th gestational months short GAP-43-ir fiber bundles indicating axonal growth can be demonstrated at the inferior margin of the basolateral amygdaloid nuclei. These fiber bundles are in the vicinity of the GE and should be considered when investigating alterations of the GE, for instance as a result of hemorrhage (see "Significance of the transient structures for developmental neuropathology").

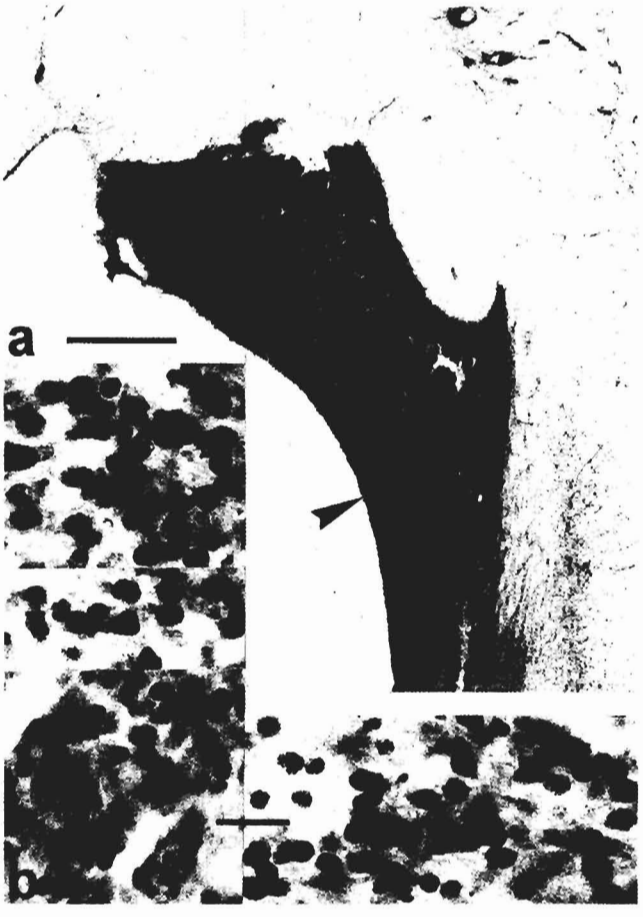


Fig. 6. a. 100-μm thick section immunostained with anti-proliferating cell nuclear antigen (PCNA), 5th gestational month. PCNA-immunoreactive cells nuclei are found in extremely high packing density in the inferior portion of the ganglionic eminence, marked by an arrowhead, subjacent to the amygdala (A). **b.** Enlargement taken from the ganglionic eminence in a: Intensely immunostained cell nuclei are visible. Scale bars: 1 mm (a), 20 μm (b).

Gangliothalamic body

Fishell et al. (1995) showed that cortical precursor cells in the proliferative zone were not stationary, but migrated in random directions without association to radial glial fibers. They observed, however, one exception. Precursor cells did not migrate across the border between the cortical and subcortical proliferative zones of the telencephalon, i.e. precursor cells of the GE remain clearly separated from those within the cortical proliferative zone in mice. With regard to these findings the data published by Rakić and Sidman in 1969 are particularly remarkable. They found that some neurons of the human dorsal Th arise in the telencephalic GE. In their study they pointed out that the pulvinar receives such neurons of telencephalic origin and that this contribution of GE neurons to the pulvinar is restricted to the human brain. Recently, these original data have been extended and partly modified. Letinić and Kostović (1997) could show that various thalamic nuclei, along the entire antero-posterior axis of the Th, are potential recipients of GE-neurons. Kornack et al. (1993) could identify clones of cells migrating from the GE to the posterior Th in the monkey brain. Most probably the number of such cells in monkey is relatively small in comparison to the human brain. Thus, there seems to be an evolutionary trend in telencephalon-to-diencephalon cell migration. Those GE-neurons destined for the dorsal

Th migrate across the telencephalo-diencephalic boundary, the terminal groove, and through a distinct transient fetal structure, referred to as the gangliothalamic body (GTh). This GTh represents a thin stripe of cells which appears as a stream of migratory neurons. The neuronal character of these cells has been shown by their expression of the neuron-specific marker MAP2. The bipolar neurons reveal the typical morphology of migrating nerve cells. The GTh which can clearly be delineated from the adjacent thalamic nuclei is well developed between the 18th and 34th gestational week (Letinić and Kostović, 1997). Generation of neurons in the proliferative zone of the diencephalic vesicle ceases, however, long before the

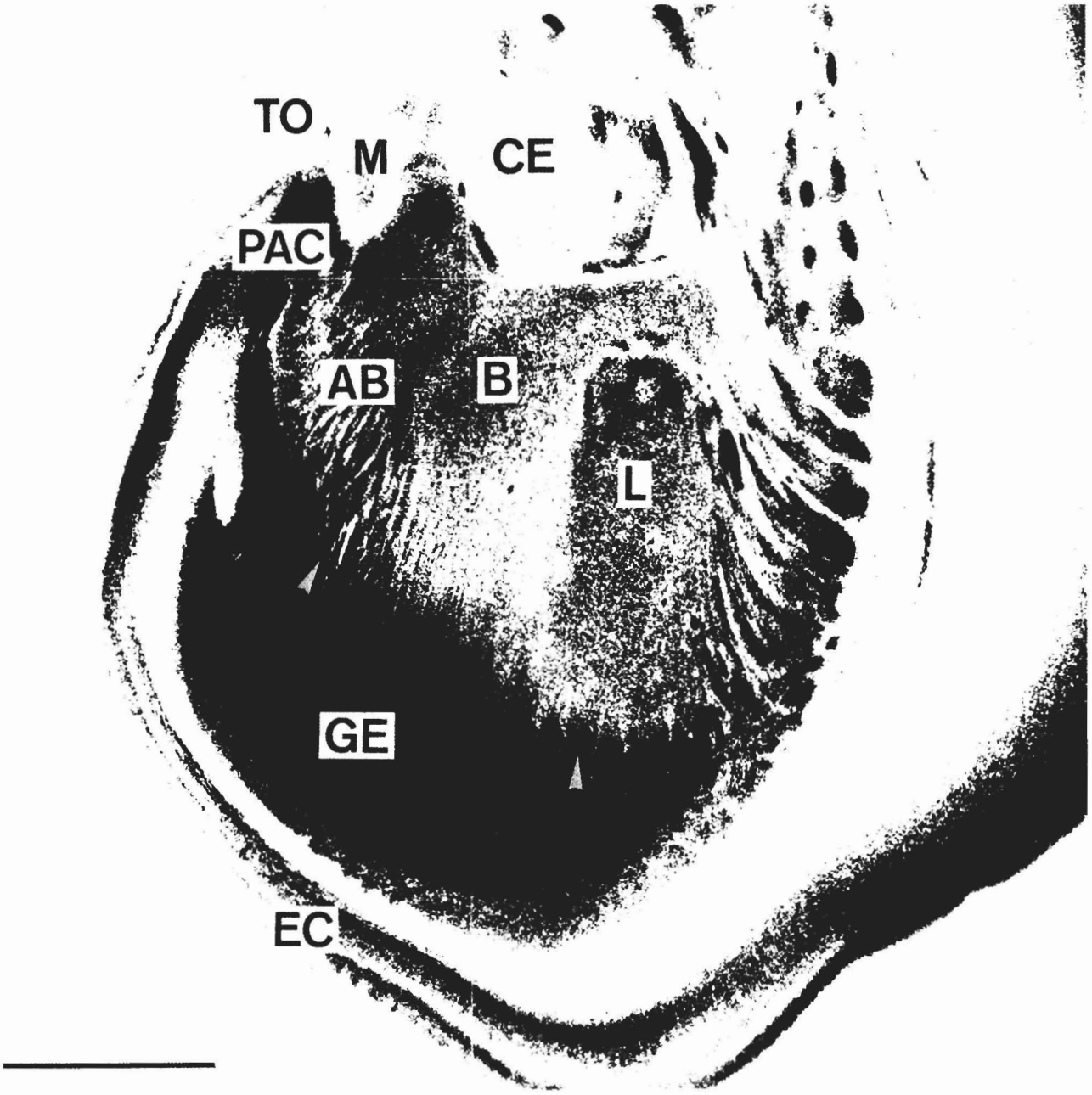


Fig. 7. Frontal section (100 μm thick, Nissl-stained) of the amygdaloid nuclei in the 5th gestational month. Note the prominence of the ganglionic eminence (GE) and the column-like cell aggregations at the inferior margin of the basolateral amygdaloid nuclei (accessory basal nucleus, AB; basal nucleus, B; lateral nucleus, L); these columnar cell clusters extend into the GE (marked by arrow heads). Scale bar: 1 mm. Reproduced with permission from Ulfig et al., 1998d (Karger, Basel).

18th week. The lateral margin of the GTh is located next to terminal groove (telencephalic-diencephalic sulcus) where the GTh merges with the medial edge of the GE. It lies upon the superior thalamic nuclei in the lateral third or lateral half. The GTh cannot be delineated in the monkey brain due to the small number of GE neurons migrating to the Th. It still has to be elucidated whether the thalamic neurons arising from the GE belong to a certain neuronal class (for instance interneurons) or have another characteristic in common in the adult brain.

Distinguishing characteristics

As mentioned above GE cells and cortical precursor cells do not intermix so that a boundary between the two proliferative zones can be expected. In a recent study the transcription factor, Pax6, has been shown to be involved in the formation of this boundary (Stoykova et al., 1997). These authors demonstrated that the boundary is distinctly altered in Pax6 mutant mouse; for instance, the normal expression of tenascin-C at the border is lost. In another study the precursor cells from the GE and the cortical proliferative zone have been shown to segregate from each other in a short-term aggregation assay (Götz et al., 1996). In this paper the authors postulated that the segregation is Ca^{2+}-dependent and is probably mediated by the CD 15 carbohydrate epitope which is expressed by cortical but not by GE precursor cells.

Another distinct difference between cortical and GE precursor cells has been pointed out by Birling and Price (1998). They found that the potential to generate oligodendrocytes is significantly greater in GE precursor cells. As a consequence of the reduced potency of cortical precursor cells to generate oligodendrocytes GE precursors destined to become oligodendrocytes have been postulated to migrate into cortical areas (Birling and Price, 1998).

Another characteristic that distinguishes the GE from the cortical proliferative zone is the expression of retinoids in glial (probably radial glial) cells within the lateral but not medial GE (Toresson et al., 1999). These authors also provided evidence that retinoid signalling within the lateral GE is involved in the differentiation of striatal nerve cells.

In a recent study the medial GE, the lateral GE and the cortical proliferative zone have been shown to have unique migratory potentials (Wichterle, 1999). Cells of the medial GE can migrate extensive distances. This remarkable ability of precursor cells can only be attributed to medial GE cells.

Although there seems to be a distinctive boundary separating the compartment of lateral GE cells from that of the cortical precursors, GE cells have been demonstrated to contribute significantly to the ventrolateral cerebral cortex (Stensaas and Gilson, 1972; Bayer and Altman, 1991; De Carlos et al., 1996). In line with these experimental data glial processes have been shown to be arranged in a manner that allows them to guide migrating neurons from the lateral GE to the ventrolateral cortex (Smart and Sturrock, 1979).

Do the subplate, the perireticular nucleus and the ganglionic eminence share a common characteristic?

Recently, Métin and Godement (1996) showed that the GE may be an intermediate target for corticofugal and thalamocortical fibers. On their way towards their target regions both thalamic and cortical axons seem to pause within the GE (i.e. mainly within the mantle region of the GE). Cells of this mantle region send transient early projections towards the cortex and the Th. Thus, this mantle region appears to fulfil developmental functions which are very similar to those of the PR and the SP. The cortex is reached by early projections from the cells of lateral GE which most probably correspond to the transient CB positive nerve cells described earlier (Liu and Graybiel, 1992). The medial GE sends fibers towards the PR. These differential projections of the medial and lateral GE match with the differential expressions of developmental genes: Gbx2 is expressed in the medial GE and the Th, whereas Otxl and Otx2 are found in the lateral GE and the cortex.

The mantle region of the GE contains postmitotic neurons characterized by a complex morphology. These neurons receive transient afferents (from the cortex and the Th) and may constitute an intermediate target which reveals reorientation of growing fibers, occurrence of complex growth cones and axocellular contacts (Métin and Godement, 1996).

Corticofugal axons make a turn at the ventricular angle which is located near the lateral GE. This turn in the course of the fibers may indicate a change in guidance cues in this location (Métin and Godement, 1996). As has been shown in transplantation and culture experiments the lateral GE induces rapid and extensive outgrowth of cortical axons and attracts these axons (Métin et al., 1997). These effects have been demonstrated to be mediated by netrin-1, a bifunctional molecule which can promote the outgrowth of commissural axons and can attract their growth cones towards the midline (Shirasaki et al., 1995; Serafini et al., 1996). During early development netrin-1 is expressed in all cells of the lateral GE, particularly in those forming the medial portion of the lateral GE (Métin et al., 1997). During later developmental stages netrin-1 expression is restricted to mantle cells of the lateral GE, i.e. those postmitotic cells that are thought to represent an intermediate target for growing fibers (see above). It is tempting to assume that the corticofugal fibers may be waiting at the GE for interactions with thalamocortical axons ("handshake hypothesis").

Taken together, additional studies are necessary to determine the exact sequence in the occurrence of transient connections, their exact origins and targets, the mechanisms involved in axonal growth, and the relative contribution of the various transient projections to the

establishment of mature connections.

Significance of the transient structures for developmental neuropathology

Various studies have clearly demonstrated that SP neurons play a pivotal role in coordinating various developmental events that finally lead to mature connections, in particular between the thalamus and the cerebral cortex. Moreover, the SP-layer is an outstandingly wide zone in the human fetal brain, and the SP/CP ratio is 4:1 during the peak development of the SP. In spite of this functional and morphological prominence the SP is only seldom considered adequately in neuropathological studies.

Kostović et al. (1989) demonstrated the rapid development of anechoic cavities in the SP of premature brains. The vigorous development of these cavities has been attributed to the huge amount of ECM encountered in the SP. These authors also showed that the cavities disappeared around the 11th postnatal month and they postulated that the SP neurons and waiting afferents recover.

Recently Volpe (1996) has commented on the possible importance of SP neurons in brain injury of the premature infant. The peak of development of the SP closely corresponds to the time frame when ischemic lesions occur in preterm infants. Thus, the important developmental functions of the SP could be impaired due to discrete alterations in this zone. This assumption would enable one to find a morphological substrate of cognitive deficits. The latter occur in as many as 25% to 50 % of small premature infants.

Alterations in the neuronal composition of the WM have been demonstrated in schizophrenics. Using NADPH-d (nicotinamide adenine dinucleotide phosphate diaphorase) histochemistry an increased number of NADPH-d-positive neurons have been found deep in the WM (Akbarian et al., 1993a). Moreover, a displacement of MAP2-immunoreactive neurons and neurons immunostained by an antibody against a non-phosphorylated epitope of the 160 kDa and 200 kDa neurofilament protein has been demonstrated (Akbarian

Fig. 8. Frontal section, 100 μm thick, Nissl-stained, 7th gestational month. Note the bleeding within the gangliothalamic body, marked by arrows. It lies upon the superior thalamic nuclei. The thin gangliothalamic body laterally borders upon the telencephalic-diencephalic sulcus (marked by an arrow head). In this location the gangliothalamic body merges with the medial edge of the ganglionic eminence. Scale bar: 1 mm.

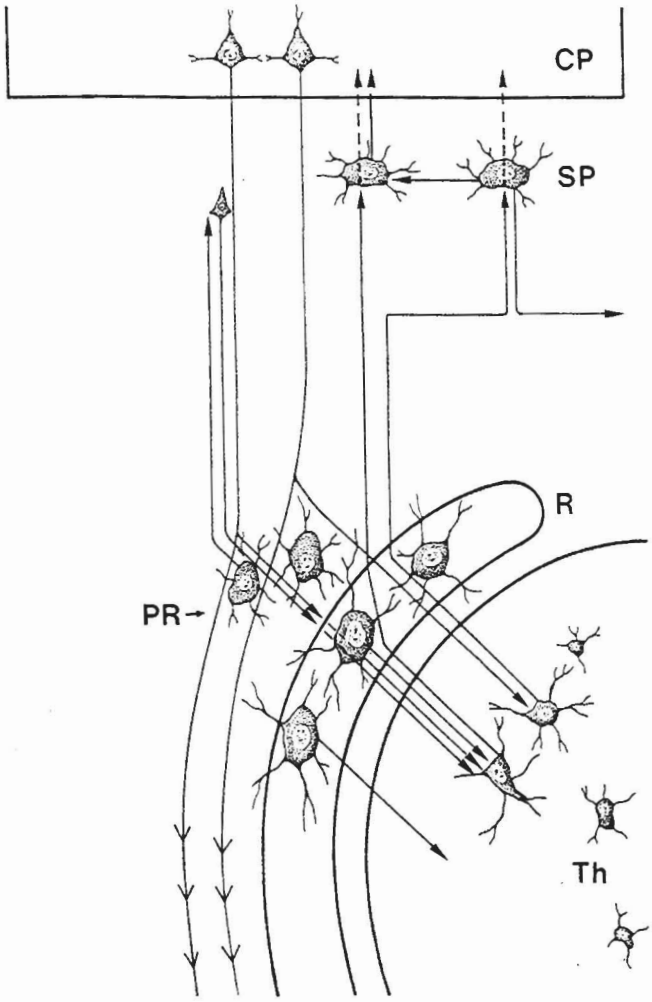


Fig. 9. Fetal neuronal circuitries and interactions between the cortical plate (CP), subplate (SP), perireticular nucleus (PR), thalamic reticular nucleus (R) and dorsal thalamus (Th). For details, see text.

et al., 1993b). These neurons were also encountered in significantly higher number in the deep WM of schizophrenics (prefrontal cortex) in comparison to controls. As the number and density of nerve cells in the overlying cerebral cortex have been shown to be unchanged, a disturbance of neuronal migration to the cortex does not appear to account for the alterations in the density of deep interstitial neurons. The mechanism leading to the changes in the WM of schizophrenics may involve a disturbance in the primary formation or in the resolution of the SP.

It is tempting to assume that discrete alterations of neuronal circuitry which may play a role in the pathophysiology of schizophrenia occur due to developmental disturbances within the SP. Changes in the cellular composition of the SP or in the distribution pattern of the neurons may lead to a failure in appropriate invasion of afferent fibers. In accordance with these considerations a shift of dopaminergic afferents from pyramidal to non-pyramidal neurons has been postulated recently in schizophrenia (Benes, 1998). It is a challenging task to further investigate human interstitial neurons and the human SP in more detail using different markers which could reveal functional aspects (Ulfig, 1999). Such data would provide a basis for studies on subtle alterations occurring in the WM of schizophrenics.

Intrauterine infection representing a leading cause of preterm labor is accompanied by elevated concentrations of cytokines in the amniotic fluid and umbilical cord plasma (Watts et al., 1992; Hampl et al., 1995; Reimer et al., 1999). Concentrations of the multifunctional inflammatory cytokine IL-6 have been shown to be significantly increased in cases of intracranial hemorrhage (ICH) (Weeks et al., 1997). The latter is one of the most frequent CNS complications in immature infants and is most commonly located in the GE. The high expression of IL-6 receptor in the GE (see "Ganglionic eminence"), particularly until the 28th gestational week (Ulfig and Friese, 1999), may be the link between elevated IL-6 blood concentrations and the occurrence of ICH, particularly in very young premature infants who display a higher incidence of ICH which is more severe (Volpe, 1995). The tenuous GE capillaries which lack sufficient support from their microenvironment may rupture as a result of alterations in cerebral blood flow (Shankaran, 1997). IL-6 may then activate the immature GE cells to secrete plasminogen activator which induces an increase in fibrinolytic activity within the GE (Gilles et al., 1971; Volpe, 1995). As a result, fibrin can be lysed and large bleedings may develop from small capillary hemorrhages.

Until now there are no data available as to whether ICH in the GE has any consequences on the process of myelin formation. As has been pointed out in "Ganglionic eminence" the GE has a high potential to generate oligodendrocytes. The formation of myelin sheaths within the prosencephalon occurs according to a timetable which shows that motor nuclei reveal myelin before sensory nuclei. Moreover, it has been demonstrated that myelin formation is altered due to external influences (malnutrition, Ulfig et al., 1998c). Recently, glutamate has been shown to be highly toxic to oligodendrocytes (Oka et al., 1993). This observation could explain the loss of oligodendrocytes occurring in areas where injury as a result of periventricular leukomalacia (PVL) leads to an axonal disruption (Volpe, 1995). Thus, high concentrations of glutamate could be released. It would therefore be interesting to investigate any alterations in the spatio-temporal pattern of myelin formation as a result of ICH as well as PVL. PVL representing an ischemic lesion of the white matter and occurring mainly in preterm infants may also involve the internal capsule which includes the PR (Kinney and Armstrong, 1997). Thus, the developmental function of this structure may also be impaired in PVL.

Bleedings in the ganglionic eminence may, moreover, result in a destruction of astroglial precursor cells and of the radial glial scaffold through injury of the radial glial somata being located in the GE. Moreover, the function of the GE as an intermediate target may be impaired. As demonstrated in Fig. 8, GE-bleedings can extend into the GTh thus thalamic precursor neurons may be damaged. If bleedings are localized in the inferior portion of the GE, i.e. in the vicinity to the A, they could disturb the neuronal development of the A. Recently, it has been shown that small CR- and CB-neurons displaying the shape and orientation of migrating neurons are seen in the A close to the GE in the 6th gestational month (Setzer and Ulfig, 1999). Thus, these neurons, most probably belonging to the class of non-pyramidal interneurons, may be damaged in ICH.

On the whole, it is obvious that the transient structures described in this review are of great significance in developmental neurology and neuropathology.

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