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COMMENTARY

The Development of Hippocampal Interneurons in Rodents

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ABSTRACT: Interneurons are GABAergic neurons responsible for inhibitory activity in the adult hippocampus, thereby controlling the activity of principal excitatory cells through the activation of postsynaptic GABAA receptors. Subgroups of GABAergic neurons innervate specific parts of excitatory neurons. This specificity indicates that particular interneuron subgroups are able to recognize molecules segregated on the membrane of the pyramidal neuron. Once these specific connections are established, a quantitative regulation of their strength must be performed to achieve the proper balance of excitation and inhibition. We will review when and where interneurons are generated. We will then detail their migration toward and within the hippocampus, and the maturation of their morphological and neurochemical characteristics. We will finally review potential mechanisms underlying the development of GABAergic interneurons. © **2006 Wiley-Liss, Inc.**

KEY WORDS: hippocampus; development; interneuron; GABA; migration; synaptogenesis; GABAergic synapses; calcium-binding proteins; neuropeptides

INTRODUCTION

Interneurons are local circuit neurons responsible for inhibitory activity in the adult hippocampus, thereby controlling the activity of principal excitatory cells, i.e., pyramidal cells in the hippocampus proper and granule cells in the dentate gyrus (Fig. 1). The morphological and physiological characteristics of adult hippocampal interneurons have been very precisely reviewed (Freund and Buzsaki, 1996, Somogyi and Klausberger, 2005). Only their main characteristics will be presented in this introduction. Although some glycinergic synapses have recently been described in the hippocampus (Danglot et al., 2004), hippocampal interneurons are characterized by the synthesis and release of the neurotransmitter γ-aminobutyric acid (GABA). Mossy cells are involved in local circuits, but they use glutamate as neurotransmitter and are therefore not considered as interneurons. Granule cells of the dentate gyrus are also local circuit neurons. However, they are excitatory glutamatergic neurons that express only transiently the GABA synthesizing enzyme Glutamic Acid Decarboxylase (GAD; Erlander et al., 1991) and the vesicular GABA transporter during development (Gutierrez, 2005). Therefore, they will also not be considered here. Interneurons exert their inhibitory control on the activity of glutamatergic neurons through the activation of postsynaptic GABAA receptors. Interneurons are activated by excitatory afferents or by nearby glutamatergic neurons. Thereby, GABAergic interneurons establish local feedforward and feedback inhibitory circuits, respectively. GABAergic synapses made by interneurons constitute only about 5% of the synapses on a pyramidal neuron of the CA1 field (Megías et al., 2001). Nevertheless, the control that they exert is crucial for the proper functioning of the hippocampus. Thus, reducing the strength of GABAergic inhibition by the application of GABAA receptor antagonists to hippocampal slices induces the appearance of a synchronous, epileptiform activity of pyramidal neurons (Miles and Wong, 1983). On the other hand, potentiation of the effects of GABA at GABAA receptors by treatment of adult rats with the benzodiazepine diazepam impairs hippocampus-dependent memory tasks (McNaughton and Morris, 1987). Hence, the level of inhibition exerted by GABAergic neurons must fit within an appropriate window to allow a proper control of glutamatergic activity. In addition, the divergence of their axonal arborization, which allows one interneuron to contact several hundreds of pyramidal neurons (Sik et al., 1995), endow them with the capability to synchronize the activity of glutamatergic neurons and to play a fundamental role in shaping the temporal pattern of various kinds of oscillatory activities (Cobb et al., 1995; Freund and Buzsaki, 1996; Somogyi and Klausberger, 2005).

Hippocampal interneurons are classified into several subgroups according to their axonal projection pattern, rather than by the shape of their cell bodies that is highly heterogeneous. Indeed, subgroups of hippocampal interneurons establish connections with specific parts of the principal neurons (Freund and Buzsaki, 1996; Parra et al., 1998; Fig. 2). Thus, basket cells make synapses specifically with the cell bodies and proximal dendrites of principal cell, while chandelier or axo-axonic cells contact the axon initial seg-

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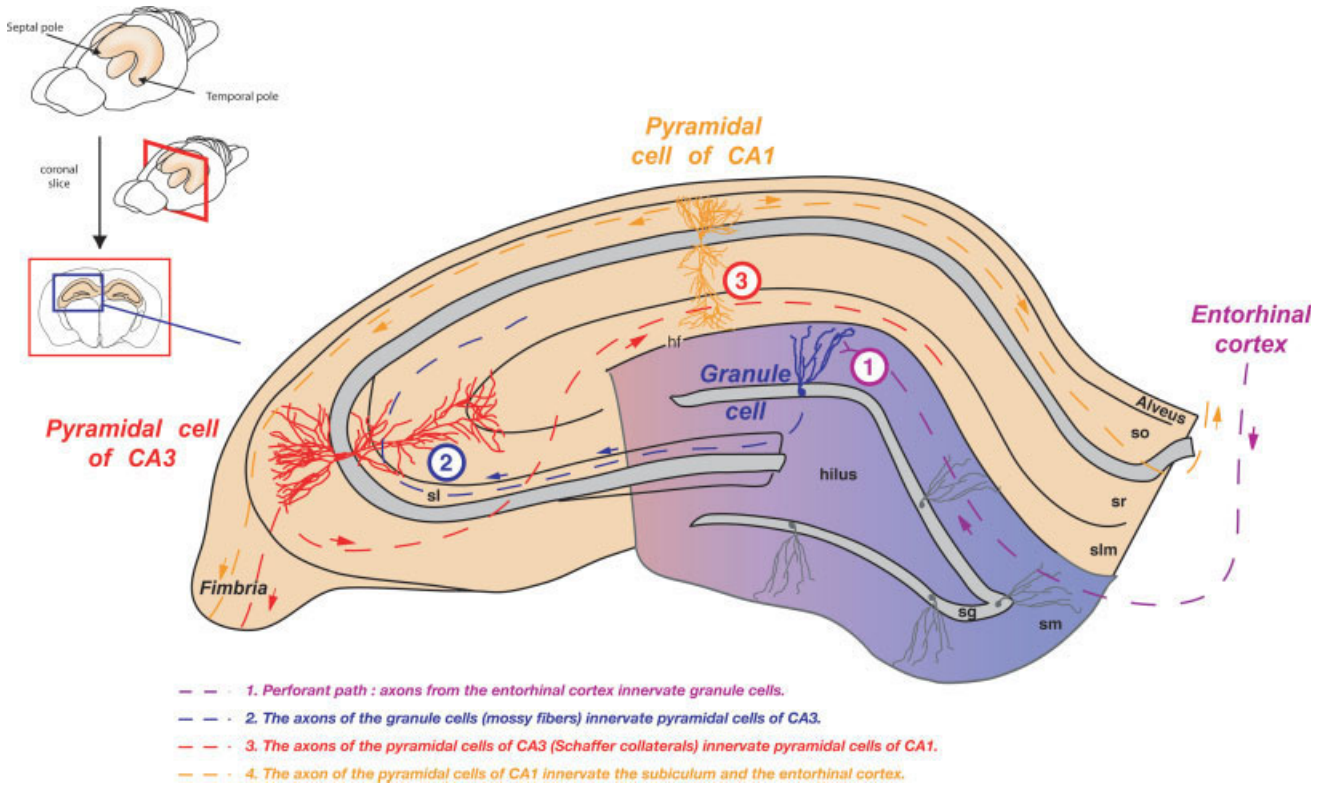

FIGURE 1. Major excitatory connections in the rodent hippocampus: the tri-synaptic circuit. The Ammon's horn is in light orange, whereas the dentate gyrus is in blue. The entorhinal cortex (EC) projects through the perforanth path on the distal two thirds of granule cell dendrites in stratum moleculare (sm), and on the distal-most part of the apical dendrites of pyramidal cells in stratum lacunosum-moleculare (slm). Mossy fibers from granule cells innervate the pyramidal cells of CA3 in stratum lucidum (sl). The axons of CA3 pyramidal cells (Schaffer collaterals) then innervate CA1 pyramidal cells, which in turn innervate back the EC, and the subiculum. hf: hippocampal fissure; sg: stratum granulosum; slm: stratum lacunosum-moleculare; sm: stratum moleculare; so: stratum oriens; sp: stratum pyramidale; sr: stratum radiatum.

ment of principal neurons (Lorente de Nó, 1934; Kosaka, 1983; Somogyi et al., 1983; Ramón y Cajal, 1995). Other interneurons target specific parts of the dendrites of pyramidal neurons. The most striking examples are the oriens-lacunosum-moleculare (O-LM) cells, which are located in the stratum oriens but contact the distal-most part of the apical dendrites of pyramidal neurons in the stratum lacunosum-moleculare (Lorente de Nó, 1934; Ramón y Cajal, 1995). These various interneuron subtypes may differentially affect the activity of excitatory neurons. Inhibitory synapses on cell bodies or axon initial segments are ideally located to control the genesis of action potentials, while interneurons targeting the dendrites of pyramidal neurons may control dendritic calcium spikes (Miles et al., 1996). Thus, O-LM cells may control excitatory inputs from the entorhinal cortex, which also terminate specifically on the distal-most part of the apical dendrites of pyramidal neurons (Fig. 2). In addition, different subtypes of interneurons may be involved in shaping specific oscillatory activities, owing to their particular spiking characteristics and axonal projections (Gloveli et al., 2005).

Interneurons also establish inhibitory synapses with other interneurons. A particular subgroup of GABAergic neurons is specialized in the control of other interneurons (interneuron-selective inhibitory cells: IS-1, IS-2, and IS-3; Fig. 2; Acsády et al., 1996a,b; Gulyás et al., 1996; Hájos et al., 1996). Furthermore, basket cells establish synapses not only with the cell bodies and proximal dendrites of principal neurons but also with other basket cells (Fukuda and Kosaka, 2000). Basket cells are interconnected by electrical and chemical synapses (Fukuda and Kosaka, 2000; Venance et al., 2000). Similarly, neuroglia-form interneurons in the stratum lacunosum moleculare of CA1 contact each other through both chemical and electrical synapses (Price et al., 2005). Hippocampal interneurons also receive a GABAergic innervation originating from the septum (Freund and Antal, 1988), which is the septohippocampal pathway. Some GABAergic hippocampal interneurons are also not "true" local circuit neurons since they project out of the ipsilateral hippocampal formation. These interneurons can be classified in two categories: interneurons with a commissural projection and interneurons innervating the medial septum. Retrograde tracing and GAD immunohistochemistry have shown that the hippocampal commissural pathway contains a minor GABAergic inhibitory component, originating from the hilus and the CA3 and CA1 areas (Seress and Ribak, 1983; Ribak et al., 1986). The GABAergic hippocamposeptal pathway is composed of interneurons located in stratum oriens and

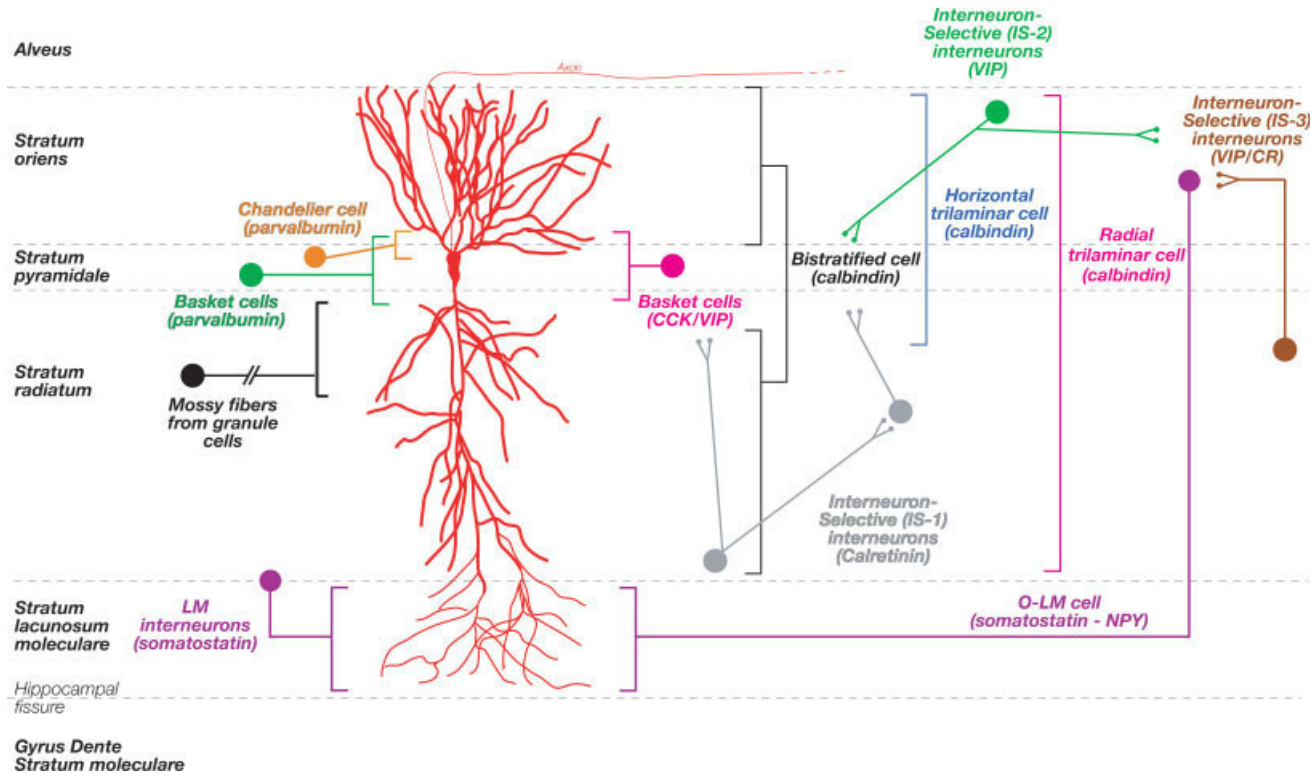

FIGURE 2. Schematic representation of the GABAergic afferences on hippocampal pyramidal cells. Interneurons can be classified either by their calcium-binding protein content, or by their axonal arborization. For clarity, dendritic arborizations of interneurons have been omitted. Plain circles correspond to soma, and vertical hooks indicate the zone of the pyramidal cell receiving the GABAergic input. Below each interneuron type, calcium-binding protein and neuropeptide content is indicated into parenthesis. Bistratified cells (containing CB) innervate the dendrites of pyramidal cells. LM and O-LM cells, which express SOM, innervate the distal portion of pyramidal cell dendrites in stratum lacunosum moleculare. PV-containing interneurons innervate the soma (basket cells) or the initial segment of the axon (chandelier cells) of pyramidal cells. Another type of basket cell expresses CCK and VIP instead of PV. Some interneurons are dedicated to the inhibition of other interneurons (IS 1, 2, and 3). The soma of IS interneurons have been arbitrary represented in different strata, but each category can be found either in stratum oriens, pyramidale or radiatum. The localization of the synapses between IS interneurons and their targets are not exhaustive since many combinations are possible. IS-1 interneurons innervate interneurons contacting the dendrites of pyramidal cells, CCK/VIP basket cells and other IS-1 interneurons. IS-2 cells innervate both interneurons contacting the dendrites of pyramidal cells and IS-3 interneurons. IS-3 interneurons innervate O-LM interneurons. This scheme has been inspired from several figures in Freund and Buszaki (1996). CCK, cholecystokinine; CR, calretinin; IS, interneuron-selective; LM, lacunosum-moleculare; NPY, neuropeptide Y; O-LM, oriens-lacunosum-moleculare; VIP, vasoactive intestinal polypeptide.

hilus (Alonso and Köhler, 1982) that innervate GABAergic neurons in the medial septum and the diagonal band of Broca (Toth et al., 1993). The interconnection of GABAergic neurons may be crucial for their effects on oscillations.

Interneurons with specific projection patterns also express particular calcium-binding proteins or neuropeptides (Freund and Buzsaki, 1996; Fig. 2). Thus, chandelier cells and the most important subgroup of basket cells express the calcium-binding protein parvalbumin (PV; Kosaka et al., 1987; Katsumaru et al., 1988). Another group of basket cells express the neuropeptides cholecystokinine (CCK) and vasoactive intestinal polypeptide (VIP), as well as the cannabinoid receptor CB1 (Katona et al., 1999). In contrast, the calcium-binding protein calbindin (CB) or the neuronal nitric oxide synthase enzyme are expressed by interneurons contacting the dendrites of pyramidal neurons (Gulyás and Freund, 1996; Seress et al., 2005). Besides its particular somatic localization and axonal projection, the O-LM cell is also characterized by the expression of the neuropeptide somatostatin (SOM; Freund and Buzsaki, 1996). Interneuron-selective inhibitory cells express the calcium-binding protein calretinin (CR) or the neuropeptide VIP (Acsády et al., 1996a,b; Gulyás et al., 1996; Hájos et al., 1996). However, the expression of a particular calcium-binding protein or neuropeptide may not be sufficient to allocate an interneuron to a particular subgroup. Indeed, several classes of interneurons often express the same molecule (Somogyi and Klausberger, 2005). Furthermore, although interneurons can be classified according to their axonal projection, an additional diversity can be found when their firing pattern and response to modulating transmitters is taken into account (Parra et al., 1998). Thus, hippocampal interneurons cannot be easily ordered in a few well-defined groups when several criteria are taken into account.

The great accuracy of both the topography of inhibitory connections and the balance of excitation and inhibition indicate that the development of hippocampal interneurons is likely

controlled by several distinct mechanisms. The specificity of inhibitory connections suggests that particular interneuron subgroups are able to recognize molecules segregated on the membrane of the pyramidal neuron. Once specific inhibitory connections have been established, a quantitative regulation of their strength may then be performed to achieve the proper excitatory-inhibitory balance. Knowledge of the sequence of events leading to the establishment of the adult inhibitory circuitry is a prerequisite to set up experiments aimed to elucidate the underlying mechanisms. We will first review when and where interneurons are generated. We will detail their migration toward and within the hippocampus, and the maturation of their morphological and neurochemical characteristics. We will then review potential mechanisms underlying the development of GABAergic interneurons.

ORIGIN AND MIGRATION OF HIPPOCAMPAL INTERNEURONS

Hippocampal Neurogenesis

Early studies aimed to identify the origin and the route of migration of hippocampal neurons, independantly of their excitatory or inhibitory nature. Altman and Bayer (1990a) investigated the development of the rat hippocampus at short and sequential survival times after (^{3}H)thymidine injections, in order to identify the neuroepithelial sources of the various neuronal populations, and to follow their route of migration and order of settling. These studies allowed the identification of three discrete components constituting the hippocampal neuroepithelium (Fig. 3): the first one (ammonic neuroepithelium) is the origin of pyramidal cells and large neurons of stratum oriens and radiatum, the second one (dentate neuroepithelium) generates granule cells and large neurons of stratum moleculare and hilus, whereas the last one is a glioepithelium that produces the glial cells of the future fimbria. In the rat, pyramidal cells are generated between embryonic day 16 (E16) and E19, with a peak for CA3 (E17) before CA1 (E19). In mice pyramidal neurons are generated at E14–E15 for CA3, and at E15–E16 for CA1 (Soriano et al., 1986, 1989a,b). Pyramidal cells move out of the neuroepithelium one day after their generation, and form a band of cells in the intermediate zone (IZ) (Altman and Bayer, 1990ab; see the gray band in Fig. 3). The day after, they leave this band and begin their migration towards the hippocampal plate (future pyramidal cell layer, green in Fig. 3). It takes four days to CA1 pyramidal cells to reach the hippocampal plate, and a longer time for CA3 cells due to their curved trajectory around CA1 neurons. The pyramidal cell layer is recognizable as soon as at E20 for CA1 and E22 for CA3. At the time of birth some pyramidal cells are still migrating toward the pyramidal cell layer. The granule cells of the dentate gyrus are generated very late, since 85% are generated postnatally, from which 10% are born after P18 (Fig. 8). Their genesis starts at E20 with a peak during the first postnatal week (Bayer, 1980a; Altman and Bayer, 1994). The dentate gyrus starts to be recognizable as a morphological entity at E21–E22 (Altman and Bayer, 1990c).

Bayer (1980a,b) and Altman and Bayer (1990a–c) have also described the migration of a population of large hippocampal neurons. Although their GABAergic phenotype has not been established, their final destination in the dendritic layers suggests that they are interneurons. Furthermore, these large neurons are generated before the principal cells, indicating that they are not displaced pyramidal neurons. Some of these neurons come from the ammonic primordium between E15 and E17 and invade the strata radiatum and oriens, whereas others originate from the dentate primordium between E15 and E19 and migrate in the hilus (Bayer, 1980a; Altman and Bayer, 1990a). Other studies identified the birth date of GABAergic interneurons without identifying the location of their genesis and the route and timing of their migration. They coupled (^{3}H)thymidine injections during development and immunohistochemistry for GAD. These studies indicate that hippocampal interneurons are generated prenatally in rat (Amaral and Kurz, 1985; Lübbers et al., 1985) and mice (Soriano et al., 1986, 1989a,b). In rats, the genesis of GABAergic interneurons occurs between E13 and E18 (Amaral and Kurz, 1985). In mice, interneurons are generated between E11 and E17 (Soriano et al., 1986, 1989a,b; Fig. 8). However, differences are observed between the hippocampus proper and the dentate gyrus. Most of interneurons from CA1 and CA3 are generated at E12–E13, whereas the majority of dentate gyrus interneurons originate at E13–E14 (Soriano et al., 1989a,b). Furthermore, different birth dates of interneurons are observed in a given hippocampal subfield. Thus, according to the sandwich theory, GABAergic interneurons of the plexiform layers (i.e., prospective dendritic layers: strata oriens and radiatum) are generated before interneurons of the pyramidal layer (Bayer, 1980a; Soriano et al., 1989a). In addition, and similar to pyramidal cells, GABAergic interneurons of the pyramidal layer are generated following an inside-out gradient: the oldest neurons are in the inferior portion of the layer.

Thus, the peak of genesis of rat and mouse interneurons occurs prior to the peak of genesis of principal neurons (Fig. 8). This early genesis of GABAergic neurons does not imply that they are established in definitive layer and functional before excitatory ones, since their migration and their insertion into functional electrical network have to be taken into account (see below).

Origin of Hippocampal Interneurons

Glutamatergic pyramidal cells and cortical GABAergic interneurons are divergent in both their source of genesis and their mode of migration. Glutamatergic neurons are known to originate from the neuroepithelium in the ventricular zone (VZ) of the dorsal telencephalon (isocortex and hippocampus), and to migrate radially across the IZ toward the pial surface to take their final position in the cortical or hippocampal plate. However, the origin of hippocampal GABAergic neurons is still under debate.

Studies using lineage markers and BrdU injection suggested that pyramidal neurons and GABAergic interneurons arise from different progenitors in the VZ, and adopt different patterns of migration (Parnavelas et al., 1991; Mione et al., 1994, 1997). They showed that clonally related pyramidal cells remain close to each other in several regions of the cortex. In contrast, inter-

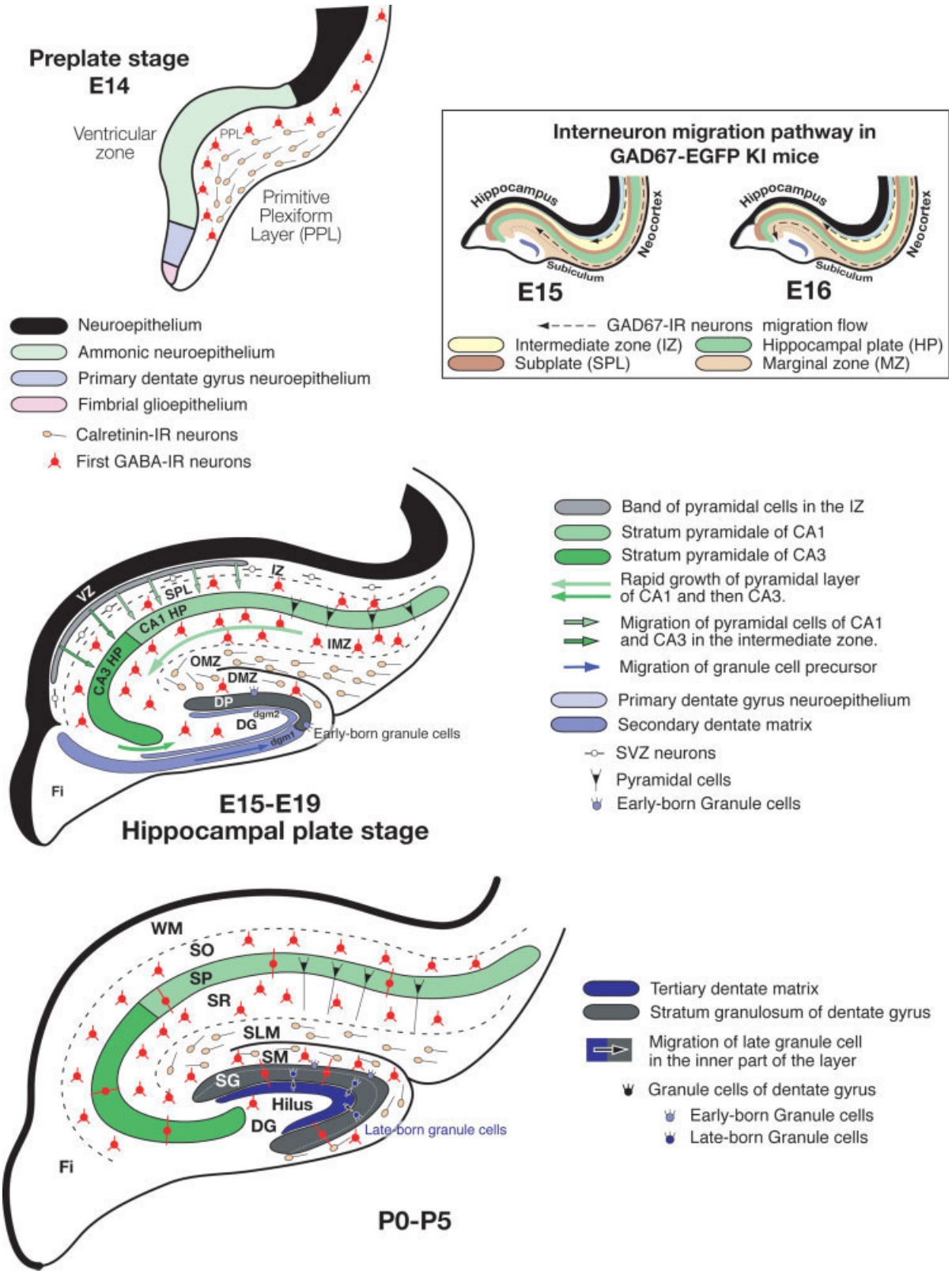

FIGURE 3

neurons were found exclusively in pairs or as single cells, suggesting that they were dispersed because of tangential migration. Later studies further demonstrated that radially arranged neurons express glutamate, the neurochemical signature of pyramidal cells, while tangentially dispersed cells are GABAergic interneurons (Tan et al., 1998). However, none of these studies examined the origin of GABAergic interneurons and it was assumed that cortical GABAergic interneurons arise from cortical proliferative regions.

Anderson et al. (1997a) provided the first evidence that GABAergic interneurons do not originate in the cortical proliferative region. At embryonic stages, the telencephalon is constituted by the pallium (roof) and the subpallium (base) (Nadarajah and Parnavelas, 2002). The pallium gives rise to the neocortex and hippocampus, whereas the subpallium gives rise to the basal ganglia (Fig. 4A). The homeobox genes Distal-less homeobox 1 and 2 (*Dlx1/2*) are expressed in the subpallium. They may induce the production of GABA and play a role in the specification of GABAergic neurons (see later). Analysis of *Dlx1/2* knock-out mice provided evidence that interneurons originate in the subpallium telencephalon and migrate tangentially to the cortex. These mice undergo a 4-folds reduction of GABAergic interneurons in the neocortex and an almost complete loss of these neurons in the hippocampus, along with a reduction in CB staining at P0 (Anderson et al., 1997a; Pleasure et al., 2000). Likewise no mRNA for the GAD67 isoform of GAD was detectable (Pleasure et al., 2000). In contrast, the other neuronal populations were not affected. Reelin and CR staining, which label Cajal-Retzius cells, appeared unchanged, and no defects in the organization and number of neurons in the granule or pyramidal cell layers were detected in the hippocampus of P0 mutant mice. Slice experiments showed that GABAergic neurons migrate from the subpallium to the striatum, neocortex, and hippocampus (Figs. 4B–D), and that *Dlx1/2* mutants have a migration defect (Anderson et al., 1997a; Marin et al., 2000; Pleasure et al., 2000). In the hippocampus Dlx2 positive cells are detected as soon as at E15.5 in the stratum radiatum, and E16.5 in the stratum oriens (Pleasure et al., 2000). Over the past few years compelling evidence has suggested that a large number of interneurons are born in the subpallial telencephalon, migrate tangentially, and populate several areas of the cortex, including the piriform cortex, the isocortex (Lavdas et al., 1999; Sussel et al., 1999; Wichterle et al., 1999), and the hippocampus (Pleasure et al., 2000, Yozu et al., 2005; for review see also Parnavelas, 2000; Corbin et al., 2001; Marin and Rubenstein, 2001, 2003; Nadarajah and Parnavelas, 2002). However, several studies have also suggested that a subpopulation of cortical interneurons could derive from progenitors located in the dorsal pallium in humans (Letinic et al., 2002) as well as in rodents (Gotz et al., 1995; He et al., 2001; Bellion et al., 2003), in agreement with the results of Altman and Bayer.

Generation of Interneuron Diversity

Different proliferative regions of the subpallium telencephalon are the origin of several structures of the adult basal telencephalon, but also give rise to interneurons populating the neo-

FIGURE 3. Neurogenesis of excitatory neurons and GABAergic investment of hippocampal layers. Most studies concerning excitatory neurogenesis have been done in rat, whereas immunohistochemical characterization of GABAergic neurons arrival has been led in mice. We have tried to summarize all processes in one scheme with mice dates, but because of the different timing of rat and mice embryogenesis it is sometimes difficult to infer precise dates. Figures are adapted with permissions from Altman and Bayer (Bayer, 1980a,b; Altman and Bayer, 1990a–c) and Soriano et al. (1986, 1989a,b). Copyright 1980, 1989, and 1990, with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Copyright 1986, with permission from Elsevier. At E13–E14, GABA-IR and CR-IR neurons are present in the plexiform layers (i.e., prospective dendritic layers). The hippocampal neuroepithelium is divided in three components: (1) ammonic neuroepithelium (light green), which will give rise to pyramidal cells and large interneurons of SR and oriens, (2) Primary dentate neuroepithelium (light blue), which will give rise to granule cells of the DG, and (3) Fimbrial glioepithelium (light pink), which produces glial cells of the fimbria (Fi). Pyramidal neurons of CA3 and CA1 are produced at E14–E15 and E15–E16, respectively. One day later pyramidal cells leave the neuroepithelium and form a band of cells in the IZ (in gray). The day after, they leave this band and it takes four days for CA1 cells to reach the pyramidal cell layer and a longer time for CA3 cells (light and dark green arrows). The primary dentate neuroepithelium gives rise to the secondary dentate matrix, from which two waves of granule cell precursors migrate toward the DG (DG migration 1 and 2—dgm1 and dgm2 in light blue). The migrating precursors retain their proliferative activity. dgm1 is the source of the earliest granule cells (light blue) that will later constitute the outer shell of the granule layer. dgm2 penetrates the basal polymorph layer and gives rise successively to the transient tertiary dentate matrix and the subgranular zone (sgz). The tertiary matrix will produce the large complement of granule cells generated postnatally that will take place in the inner part of the granule cell layer (white oulined-black arrows and dark blue granule cells). Between P20 and P30, the tertiary matrix disappears and proliferative cells are confined in the sgz at the base of the granular layer. The sgz will be the source of granule cell during all the rest of life. At E15–E19 GABA-IR and MAP2-IR neurons are located in the SVZ. GABAergic neurons are also present in the IMZ (i.e., prospective SR), whereas CR-IR cells (probably Cajal-Retzius cells) invade the outer MZ (along the hippocampal fissure i.e., prospective SM). At E15, GAD67 neurons migrating in the MZ and SVZ/IZ reach the CA1 area and the subiculum, respectively. At E16, GAD67 neurons reach CA3 from the MZ, and CA1 from the IZ. Interneurons reach the gyrus by E17 (Manent et al., 2006). During early postnatal stages neurons in the subplate and IMZ become resident cells of SO and SR, whereas CR-IR neurons of the SM disappear. DG, dentate gyrus; dgm1, DG migration (first wave); DMZ, dentate marginal zone (prospective molecular layer); DP, dentate plate (embryonic granular layer); Fi, fimbria; HP, hippocampal plate (prospective pyramidal layer); IMZ, inner marginal zone (prospective SR); IZ, intermediate zone (prospective white matter); MZ, marginal zone; OMZ, outer marginal zone (prospective stratum lacunosum moleculare); PPL, primitive plexiform layer; SG, stratum granulosum; SLM, stratum lacunosum-moleculare; SM, stratum moleculare; SO, stratum oriens; SP, stratum pyramidale; SPL, subplate (prospective stratum oriens); SR, stratum radiatum; VZ, ventricular zone; WM, white matter.

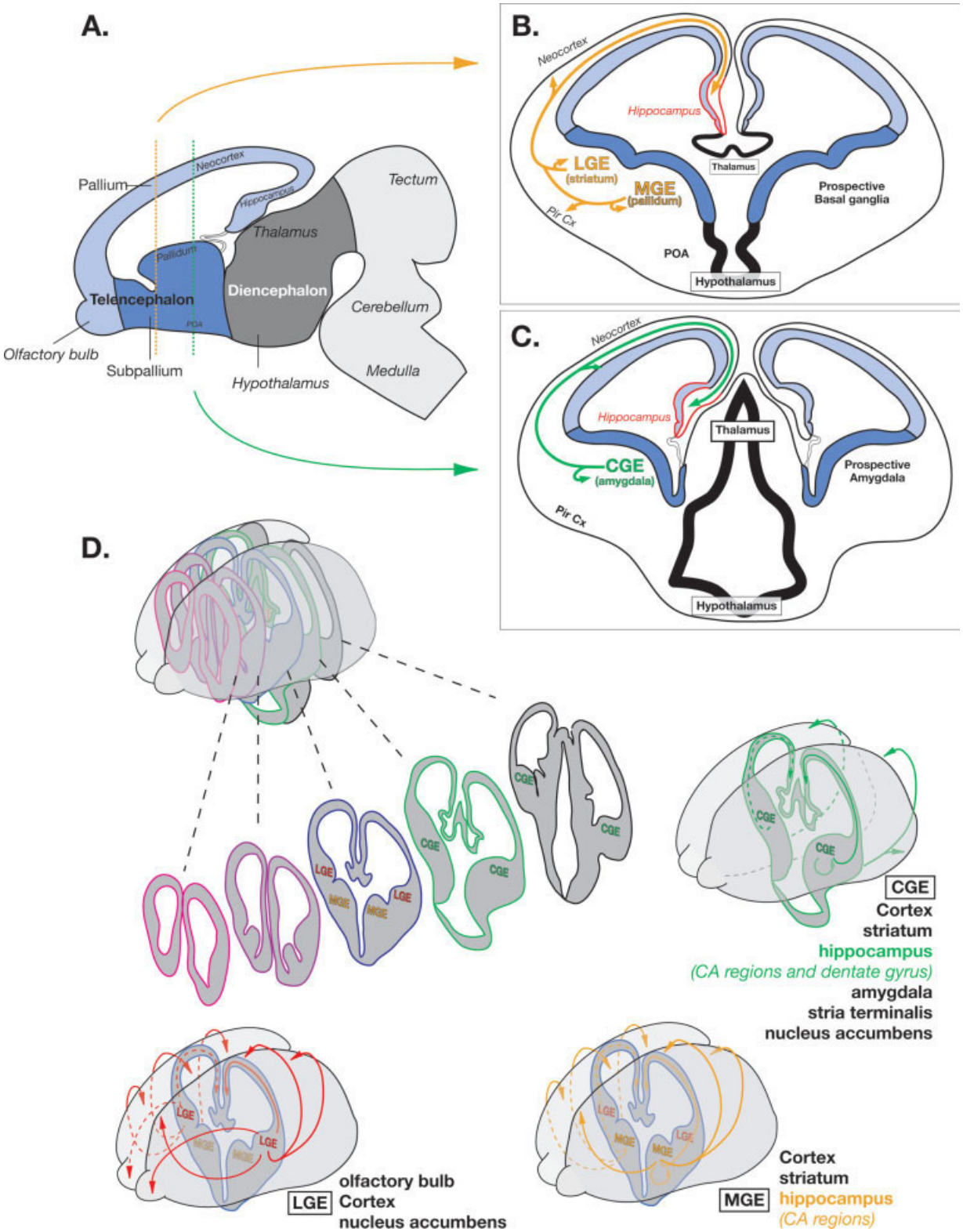

FIGURE 4. Routes of migration of interneurons from the subpallial telencephalon toward cortical and hippocampal anlage. (A) Saggital section of the rat cerebrum at E15. The plans of the coronal sections shown in (B) and (C) are indicated by orange and green vertical lines, respectively. (B–D) Coronal sections through the embryonic rat brain showing the MGE, LGE, and CGE. The MGE will give rise to the pallidum, the LGE to the striatum, and the CGE to the amygdala. Red lines delineate the hippocampus. Hippocampal interneurons are known to come from the MGE and CGE, while the LGE is a source of interneurons for the olfactory bulb, the cortex, and the nucleus accumbens. Anatomical drawings are based on data from Altman and Bayer (1995).

cortex and hippocampus during development. The Medial Ganglionic Eminence (MGE) and the Lateral Ganglionic Eminence (LGE) give rise to the pallidum and the striatum, respectively (Smart and Sturrock, 1979; Deacon et al., 1994; Figs. 4B–D). The Caudal Ganglionic Eminence (CGE) is found posterior, where the MGE and the LGE fuse into a single structure. The CGE is believed to give rise to the amygdaloid region of the limbic system (Nery et al., 2002; see for review Corbin et al., 2001). The MGE has also been identified as a source of cortical (Lavdas et al., 1999; Sussel et al., 1999; Wichterle et al., 1999; Anderson et al., 2001), striatal (Marin et al., 2000; Wichterle et al., 2001), and hippocampal interneurons (Pleasure et al., 2000), whereas the LGE is a source of interneurons for the olfactory bulb, the nucleus accumbens, and the cortex (Anderson et al., 1997a,b; Wichterle et al., 1999; Corbin et al., 2000; Anderson et al., 2001; Wichterle et al., 2001; Yun et al., 2001). Finally, the CGE produces interneurons populating the cerebral cortex, the striatum, the amygdala, the bed nucleus of the stria terminalis, the nucleus accumbens, and the hippocampus (Nery et al., 2002). The MGE produces hippocampal interneurons that will migrate to the hippocampus CA regions and avoid the dentate gyrus (Pleasure et al., 2000, Wichterle et al., 2001; Polleux et al., 2002), while the CGE generates interneurons that migrate to both the CA and the dentate gyrus regions (Nery et al., 2002). In mice expressing the Green Fluorescent Protein (GFP) under the control of the *GAD65* promoter, GFP-positive cells arise from the three GE but are mainly generated in the CGE at late stages of embryonic development (Lopez-Bendito et al., 2004).

The various proliferative regions in the subpallial telencephalon could be involved in the genesis of particular interneuron subtypes. In utero fate mapping revealed that MGE cells migrate and differentiate into a population of GABA-, PV-, or SOM-expressing neurons throughout the cortical plate (Wichterle et al., 2001). Approximately 70% of MGE-derived neurons in the neocortex were immunoreactive for PV, 35% were SOM positive, while <3% were labeled with CR antibodies. In the hippocampus, MGE-derived cells were present in CA1 and occasionally in the caudal part of CA3. Immunohistochemical analysis of the adult brain after homotypic transplants at E13.5 indicated that 29% of the CGE-derived cells expressed GABA, from which 17% were CB-positive, 27% SOM-positive, and only 3% PV-positive (Nery et al., 2002). MGE cells gave similar percentages of CB (13%) and SOM cells (26%), but a higher percentage (30%) of PV cells. Accordingly the MGE, but not the LGE, generates fast-spiking cells (Butt et al., 2005). Thus, PV-IR neurons seem to be generated mainly in the MGE. It has been shown recently that CR-IR neurons come from a distinct source. In mutants lacking the Nkx2.1 homeobox gene, a normal MGE fails to form (Fig. 5). These mice contain half of the normal number of GABA-expressing cells in the cerebral cortex (Sussel et al., 1999) and a third of the normal number of the hippocampal interneurons (Pleasure et al., 2000). Unlike *Dlx1/2* mutants, *Nkx2.1* mutants appear to completely lack cortical interneurons expressing NPY, NOS, or SOM. In the hippocampus, *Nkx2.1* mutant mice show a 2-folds decrease in the number of Dlx2 and CB expressing cells, and a lack of expression of NPY and SOM at E18.5. Unfortunately, because PV, VIP, and CCK begin to be expressed during the first postnatal week (see below), and because of the postnatal lethality of the *Nkx2.1* mutants, it was not possible to analyze in vivo the fate of these interneurons. However, in cortical cultures from these mutants no or very few cells express detectable levels of SOM, NPY, or PV, whereas CR-expressing neurons are present (Xu et al., 2004). These results suggest that PV and SOM expressing interneurons originate primarily within the MGE whereas the CR expressing interneurons derive from the CGE. These results are at variance from those of Nery et al. (2002), showing that the CGE does not give rise to CR IR neurons. It may be due to differences in the age of the embryos (E14.5 vs. E13.5 for Nery et al.) or in the portion of CGE (dorsal part vs. dorsal-and-ventral part of the CGE) used in these studies. Thus, differences in the location or timing of interneuron genesis are likely responsible for the production of different interneuron subtypes (Butt et al., 2005; Yuste, 2005). However, only few of such differences have been identified so far with respect to the great variety of interneuron subgroups.

Routes of Migration

Interneurons coming from the ganglionic eminences have been shown to migrate tangentially toward their final cortical destination by two different streams (Figs. 4 and 5): one in the subventricular zone (SVZ) or lower IZ, and another one in the marginal zone (MZ) (de Carlos et al., 1996; Lavdas et al., 1999; Jimenez et al., 2002; Polleux et al., 2002). Early born (E11.5–E14.5) neurons from the mouse MGE migrate within the IZ of the GE and disperse rapidly throughout the cortical layers whereas later born (E14.5–E16.5) neurons emerging form the MGE migrate toward the cortex within the SVZ (Anderson et al., 2001). After in utero ultrasound-directed transplantation, MGE cells migrate via the SVZ (or lower IZ) first and then in the MZ with a ratio (SVZ:MZ) changing from 3:1 to 1:6 between 2 and 4 days after transplantation at E13.5 (Wichterle et al., 2001). The authors thus proposed that MGE-derived neurons first migrate in the SVZ and then move radially into the cortical plate and MZ, where they further disperse tangentially and differentiate. MGE cells migrate through the entire cortex and into the CA fields of the hippocampus (Polleux et al., 2002). Neurons generated in the CGE also migrate to the cortex and the hippocampus by two major streams: one through the SVZ/lower IZ and a second through the MZ (Nery et al., 2002). The streams of cells do not overlap with Neurofilament-145, a marker of IZ corticofugal fibers, suggesting that interneurons do not use these fibers as a substrate for migration (but see below). While MGE cells migrate laterally and spread widely throughout the cortex (Fig. 4D), the CGE-derived cells (E12.5–E13.5) migrate caudally to the caudal-most end of the telencephalon and move toward the MZ before entering the hippocampus (Yozu et al., 2005). Neurons from the CGE were shown to migrate at 110 μm/h, which is in the same range that

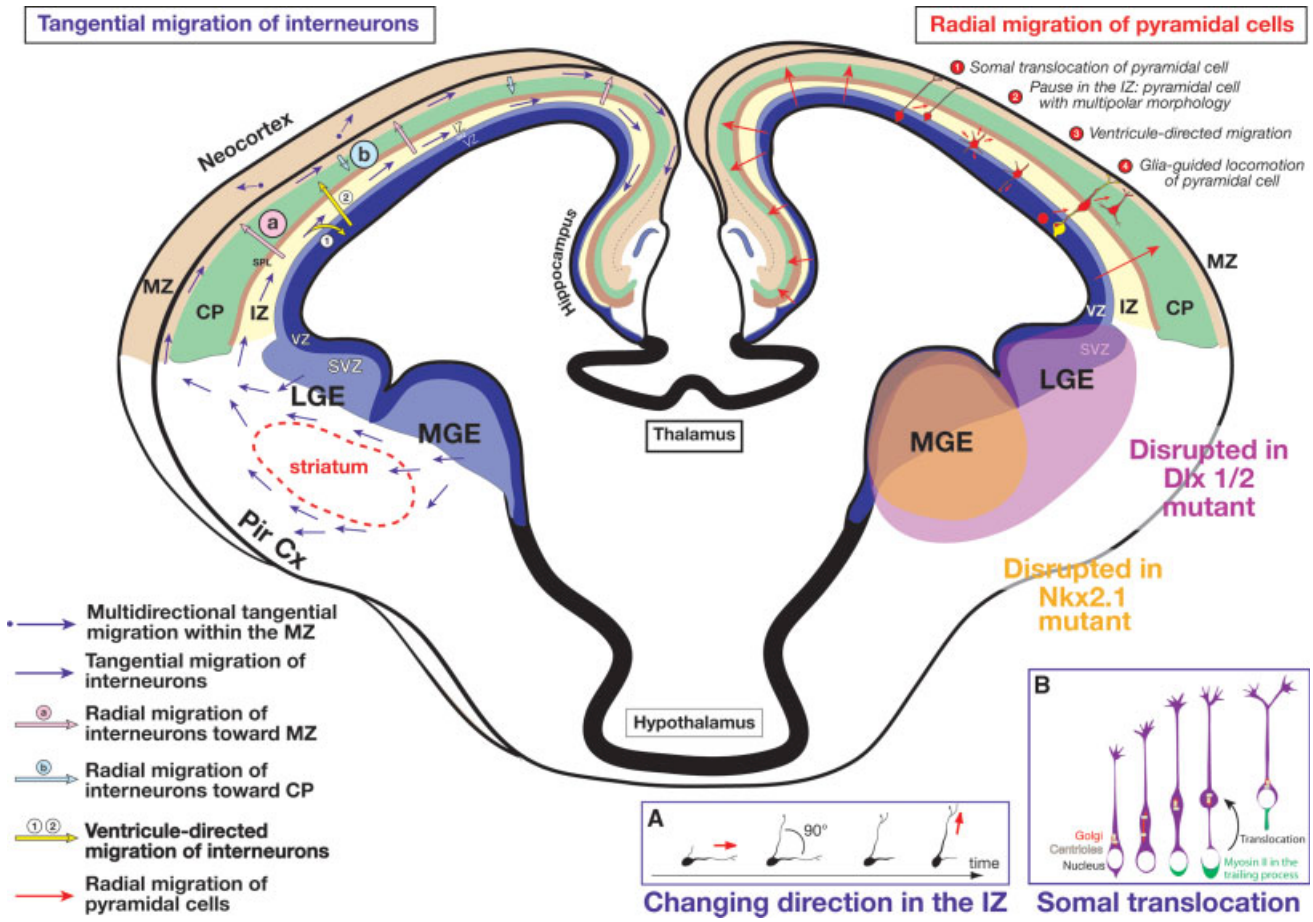

FIGURE 5. Modes of migration of interneurons and pyramidal cells of the telencephalon. Pyramidal cells originate in the neuroepithelium and migrate orthogonally toward the pial surface (right part of the figure, red plain arrows). They can adopt four different modes of migration (numbered red circle): somal translocation during early corticogenesis, glia-guided locomotion when the cortical anlage is thicker, multipolar migration at the IZ/SVZ border, and ventricule-directed migration. Most if not all interneurons are believed to come from the GE by tangential migration (left part of the figure — violet plain arrows). Interneurons from the MGE migrate to the piriform cortex, the neocortex, or the striatum. Interneurons migrating tangentially follow two different streams: one in the SVZ/IZ and another one in the MZ. Interneurons in the MZ migrate tangentially to the plane of the cortex. They can adopt various directions and thus spread all over the cortex. Some neurons in the IZ can switch to radial migration and reach the MZ (a). Conversely MZ neurons can move radially toward the CP but display a prolonged pause at the MZ/CP interface (b). Some interneurons can also adopt ventricule-directed migration (yellow arrows): they migrate toward the VZ (1), pause in the VZ, and then turn back toward the pial surface to their final destination (2). Interneurons can reach the hippocampus either by the SVZ/IZ or by the MZ stream. Insert (A): Interneurons in the IZ can change direction to reach the CP, MZ or the ventricule. They generate a leading process in the new direction and retract the former one (Polleux et al., 2002). Insert (B): Adapted, with permission, from Bellion et al. (2005). Copyright 2005 by the Society for Neuroscience. Model of nucleokinesis in MGE cells. During the resting phase of the nucleus, while the leading edge elongates, the Golgi apparatus (red) and centrioles (light brown) are associated and migrate forward up to 30 μm away from the waiting nucleus. During this movement, the centrioles split, the Golgi elongates and myosin II (green) accumulates at the rear of the cell body and pushes the nucleus toward the centrosome/Golgi apparatus. CGE, caudal ganglionic eminence; CP, cortical plate; IZ, intermediate zone; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; MZ, marginal zone; Pir Cx, piriform cortex; POA, preoptic area; SPL, subplate; SVZ, subventricular zone; VZ, ventricular zone.

speed observed for MGE derived cells (>80 μm, Wichterle et al., 2001).

Modes of Migration

Interneurons and pyramidal cells exhibit different modes of migration. Until recently it was generally assumed that excitatory pyramidal cells display radial migration, whereas interneurons adopt tangential migration. However, studies in the last 10 yr have shown that the situation is far more complex than expected. Indeed, it seems that pyramidal cells and interneurons adopt successively distinct modes of migration, which can in some cases share some troubling similarities.

Pyramidal cells originate in the neuroepithelium (VZ) and migrate orthogonally toward the pial surface (Fig. 5, right part). Three different modes of radial migration have been described in the cortex: "somal translocation," "glia-guided locomotion," and "multipolar migration" (Rakic, 1972; Shoukimas and

Hinds, 1978; Nowakowski and Rakic, 1979, 1981; Tabata and Nakajima, 2003; reviewed in Nadarajah and Parnavelas, 2002; Kriegstein and Noctor, 2004). Interneurons coming from the ganglionic eminence reach the cortex by a fourth migration mode: tangential migration (Fig. 5, left part). Once in the cortex, interneurons of the MZ and IZ/SVZ streams migrate radially or obliquely to their final localization by different ways.

Pyramidal cell migration

During early corticogenesis (formation of the preplate), somal translocation is the predominant mode of migration from the VZ toward the pial surface (Fig. 5). Neurons that migrate via somal translocation have typically a long (60–95 μm), radially oriented and often branched, leading process that reaches the pial surface, and a short trailing process. Migration is continuous and thus fast (60 μm/h). As the soma advances, the radial leading process becomes thicker. This is followed by nucleokinesis and rapid reorganization of the microtubules, leading to a shorter basal process (Nadarajah et al., 2001, 2003).

At later stages during cortical plate formation, when the cortical anlage is several hundred micrometers thick, pyramidal neurons adopt glia-guided locomotion by extending pseudopodia on radial glia fibers, which span the thickness of the cerebral wall (Fig. 5). During glia-guided migration, neurons have a shorter radial process (30–50 μm) and do not attach to the pial surface due to the thickness of the cortical anlage (reviewed in Nadarajah and Parnavelas, 2002). The length of the process is maintained during migration and the neuron moves as a single unit. It is typically bipolar, but looses its trailing process when leaving the VZ. Migration is slow (35 μm/h) and saltatory with an alternation of bursts of movements and stationary phases. Neurons using glia-guided locomotion can eventually switch to somal translocation when their radial process is near enough to the pial surface to attach to it (Nadarajah et al., 2001).

The third mode of migration, adopted by pyramidal cells when they reach the IZ/SVZ, is the multipolar migration (Tabata and Nakajima, 2003; Kriegstein and Noctor, 2004; Fig. 5). In contrast to the bipolar morphology of the two previous modes, here, neurons are transiently multipolar: they extend and retract multiple processes and do not move straight toward the pial surface. This behavior is reminiscent of the pathfinding activity of axonal growth cones. Because of this continuous change of direction, the mean migration rate of multipolar cells is about 4 μm/h, whereas the mean change in position in the radial direction is only 2 μm/h (Tabata and Nakajima, 2003).

Thus, it has recently been proposed (Tabata and Nakajima, 2003; Kriegstein and Noctor, 2004; Noctor et al., 2004) that at later stage, cortically derived neurons undergo four distinct phases of migration (Fig. 5, red circle): phase one, rapid movement to the SVZ with a bipolar morphology; phase two: a 24 h pause in the IZ-SVZ with a multipolar morphology and a capacity to move tangentially; phase three (which is optional): reversal of polarity and retrograde migration toward the ventricle; and phase four: migration to the cortical plate with characteristics of glia-guided locomotion. It should be noted that dynamic studies describing the second phase (multipolar) of pyramidal cell migration (Tabata and Nakajima, 2003; Noctor et al., 2004) are consistent with the finding of Altman and Bayer (1990a,b), which have described using tritiated thymidine labeling studies that pyramidal cells pause and form transiently a band of cells in the IZ before reaching the pyramidal cell layer.

Interneuron migration

Tangential migration. Interneurons coming from the ganglionic eminences adopt a tangential migration. The cells typically have a leading process (100–150 μm), which is often branched and tipped by growth cone (Fig. 5B). In some cases, a long and thin neurite is observed at the trailing side (Polleux et al., 2002; Bellion et al., 2005). This mode of migration shares some of the properties of the different radial modes. Indeed, interneurons exhibit a saltatory progression of the nucleus (as for the somal locomotion) and continuously extend and retract their neurites during migration (as multipolar migration). Interneuron nucleokinesis comprises two phases (Bellion et al., 2005; Fig. 5B). First, cytoplasmic organelles (Golgi apparartus and centrosome) migrate forward up to 30 μm away from the nucleus. The nucleus then translocates toward these organelles by a myosin II dependent mechanism. Nuclear displacement occurs simultaneously or immediately following a $[Ca^{2+}]_i$ increase in the leading process near the nucleus, suggesting that a localized calcium signal is necessary to elicit nucleokinesis (Moya and Valdeolmillos, 2004). During this second phase, the leading growth cone either stops migrating or divides. Migrating interneurons thus have the specific property to reposition the centrosome and the Golgi at long distance from the nucleus within the leading neurites. It suggests that the leading process shares particular relationships with these organelles. Interestingly, it has also been recently suggested that the centrosome plays a central role in the establishment of neuronal polarity (de Anda et al., 2005). After the final division, the centrosome comes to lie opposite the plane of cleavage, and the axon forms in the region where centrosome, Golgi apparatus, and endosomes aggregate. Similarly, the leading process may develop in relation with the centrosome.

Concerning the velocity, in vivo transplantation experiments have shown that interneurons migrating toward the hippocampus, i.e., 2 mm away from the site of transplantation, were observed as soon as 2 days after transplantation, which suggested a speed >80 μm/h (Wichterle et al., 2001). Polleux et al. (2002) have described a quick migration (between 58 and 140 μm/h) and Bellion et al. (2005) have measured that the speed of the nucleus could reach 130 μm/h during jumps. These values thus indicate that interneurons move faster than cells migrating along radial fibers (ranging from 10 to 35 μm/h according to Tabata and Nakajima, 2003 and Nadarajah et al., 2001, respectively) or in the first (19.7 μm/h), second (2 μm/h), or fourth phase (6.4 μm/h; Tabata and Nakajima, 2003; Noctor et al., 2004) of later migrating neurons.

Changing direction. Once arrived in the telencephalon, tangentially migrating neurons can invade the CP from either the MZ or the IZ.

In the MZ, GABAergic interneurons spread in the entire cortex via tangential migration in multiple directions (multidirectional tangential migration, Tanaka et al., 2003; Fig. 5, Left part). However, some MZ-interneurons are also able to descend away from the pial surface toward the cortical plate, while, in the mean time, other MGE interneurons migrate from the CP to the MZ (Polleux, 2002; Ang et al., 2003; Tanaka et al., 2003). In both cases (MZ > CP or CP > MZ) the migratory cells display prolonged pauses (50–70 min) at the CP/MZ interface (Polleux et al., 2002).

Similarly interneurons from the SVZ/IZ are also able to change direction to reach the CP, the MZ, or even the ventricule. A substantial fraction of IZ-interneurons have been described as deflecting obliquely from the tangential direction toward the pial surface (Tanaka et al., 2003). This is consistent with the observation that GABAergic neurons are located first in the MZ and IZ and then in the subplate and CP (Polleux et al., 2002). Similar to pyramidal cells during phase 3, IZ-interneurons are able to reverse their direction of movement by making 180° turns. These turns are not initiated by the growth cone but by a second leading process that emerges from the cell body (Polleux et al., 2002). Bellion et al. (2005) have shown that interneurons change their direction by choosing a new process where the nucleus will translocate. Thus, their capacity to change direction is directly linked to their capacity to produce diverging processes in front of the nucleus. They also showed that interneurons produce pairs of new branches by splitting their leading growth cone (Fig. 5B). Then the interneuron chooses one of the two new processes. One branch is retracted while the other will further divide and receive the nucleus. This dynamic behavior allows the neuron to integrate guidance cues from the tips of several processes over a large region (Métin et al., 2006). In hippocampal sections from *GAD67-GFP* knock-in mice, the leading process of interneurons ran below the MZ perpendicularly to radial glia extensions (Manent et al., 2006). In living hippocampal slices, rapid extensions of leading processes were followed by somal translocations.

MGE-derived cells in the IZ also frequently invade the cortical plate by making sharp 90° turns involving the generation of a new leading process in the new direction of migration (Fig. 5A). The cell body then pauses for up to 2 h before translocating and resuming its migration in the new pial direction (Polleux et al., 2002).

Ventricule directed migration. Some interneurons adopt ventricule-directed migration: from the IZ they actively migrate toward the VZ until their leading processes, with a growth cone-like structure at the tip, reaches the ventricular surface (Nadarajah et al., 2002). Then they pause in the VZ (≈45 min) while a thin trailing process appears. With time, the trailing process becomes thicker and extends toward the pia to become the new leading process. When the old leading process retracts from the VZ, the soma resumes its radial migration toward the pial surface to take its final position in the cortical anlage. This ventricule-directed migration is a saltatory movement similar to but faster (50 μm/h) than that observed with radially migrating glia-guided neurons originated at the VZ (Nadarajah et al., 2002; Ang et al., 2003). The soma usually moves rapidly up to the branched point, pauses for an extended period during which it retracts one of the processes, before resuming its movement in the direction of the remaining branch (Nadarajah et al., 2002). It is interesting to note that both interneurons (Nadarajah et al., 2002) and pyramidal cells (Kriegstein and Noctor, 2004; Noctor et al., 2004) can adopt this ventricule-directed migration before to reach their final position in the cortical mantle. The pause in the VZ may allow neurons to receive layer information. Moreover, the pauses undergone by pyramidal cells in the SVZ, and by interneurons crossing the MZ/CP or IZ/CP borders, are characterized by dynamics movements. It suggests a search of cues for migration.

Radial migration. Interneurons can then adopt radial migration as pyramidal cells do to reach their final position in the cortical plate (Tanaka et al., 2003) or the VZ (Nadarajah et al., 2002). Indeed, Polleux et al. (2002) have described that 10% of GE-derived cells found in the CP migrate radially toward the pial surface. As for glia-guided migration (Nadarajah et al., 2001), these interneurons alternate between fast and slow instantaneous rates of migration. However, it should be stressed that although interneurons make numerous contacts with radial glia fibers, their migration along radial glia is still under debate since the interneuron leading process is not always aligned with the radial glia processes. Although most of hippocampal interneurons display the typical morphology of tangentially migrating neurons in GAD67-GFP knock-in mice, some of them in the MZ also follow radial glial extensions (Manent et al., 2006). Thus, GABAergic neurons may change their mode of migration from tangential to radial to colonize the hippocampal plate, as in the neocortex.

Settling of GABAergic Interneurons in the Hippocampus

The migration of interneurons within the hippocampus was little or not investigated using real-time imaging until very recently (Manent et al., 2006). Therefore, data concerning the settling of interneurons come from analyses on fixed brains. Using *GAD67-GFP* knock-in embryos, hippocampal interneurons have been shown to colonize the hippocampal primordium by E15 (Manent et al., 2006). At this stage migrating interneurons form two distinct pathways, one superficial in the MZ in continuity with the cortical superficial stream, and the other in the SVZ/lower IZ (see insert in Fig. 3). The major stream (superficial one) carries interneurons toward the subiculum and the CA1 field, whereas the smaller deep stream stops at the border between the neocortex and the subiculum. By E16, the superficial MZ stream reaches CA3, whereas the deep stream reaches CA1 but stops at the border of CA3. Interneurons reach the dentate gyrus primordium via the superficial stream by E17.

Tangentially migrating interneurons navigate below the layer of Cajal-Retzius cells in the MZ. Between E15 and E19 GABA-positive neurons are present within the SVZ and the inner MZ (future stratum radiatum), whereas neurons positive for glutamate and CR (probably Cajal-Retzius cells) are located in the outer MZ (future stratum lacunosum moleculare) (Soriano et al., 1994; Fig. 3). Thus, characteristic neuronal populations populate each plexiform layer with no overlap. Cajal-Retzius cells are a heterogeneous population of neurons that has been implied in cortical lamination and in hippocampal development (for reviews see Meyer et al., 1999 and Soriano and Del Rio, 2005). Cajal-Retzius cells are generated at least in three focal sites (ventral pallium, septum, and hem) and are also distributed by tangential migration (Abraham et al., 2004; Bielle et al., 2005). GABAergic neurons and Cajal-Retzius cells are considered as pioneer neurons because they established synapses with hippocampal afferents at postnatal day 0 (P0–P5), before pyramidal neurons (Super et al., 1998). In agreement with their location, GABAergic neurons are the targets of early commissural axons whereas Cajal-Retzius cells are the main transient synaptic targets for entorhinal afferents. At later stages, most (75%) of the Cajal-Retzius cells and half of the GABA-positive neurons disappear from the stratum lacunosum-moleculare and stratum radiatum, and hippocampal afferents form synapses with pyramidal neurons. The marked cell loss in the stratum radiatum cannot be attributed solely to cell death. Indeed, interneurons labeled by BrdU at E13 are still present in adulthood (Jiang et al., 2001). It suggests that between P5 and P15 many GABAergic cells within the hippocampus translocate from the stratum radiatum to other laminae.

The evolution of the localization of GABA-IR neurons in the hippocampus over time is in agreement with local migrations. Indeed in the adult, most of the GABAergic soma are present in the principal cell layers or in their immediate surrounding, as well as at the radiatum-lacunosum moleculare border (Fig. 6). However at E15–E16 in the mouse, GABA-IR neurons were particularly abundant in the hippocampal and dentate MZs (prospective stratum radiatum of hippocampus and stratum moleculare of dentate gyrus) and were also present in the subplate zone (prospective stratum oriens). The hippocampal and dentate plates (prospective pyramidal and dentate granule cell layers) contained few GABAergic neurons and were also devoid of GABA-IR processes (Soriano et al., 1994). At P0, however, IR neurons were observed in the pyramidal and dentate granule cell layers. In the hippocampus, GABA-IR neurons were more abundant at the radiatum-lacunosum moleculare border and in the stratum oriens. Thus, both in the dentate gyrus and in the hippocampus proper, some of the GABA-IR neurons seemed to migrate from the dendritic to the cell body layers, and to the radiatum-lacunosum moleculare border.

A redistribution of GABAergic cell bodies was also observed after immunohistochemistry or in situ hybridization for GAD. Two isoforms of GAD, termed GAD65 and GAD67, are responsible for GABA synthesis by interneurons (Erlander et al., 1991). GAD65/67-IR was already observed at E17–E18 in the rat hippocampus, more prominently in soma of neurons located in the MZ (Dupuy and Houser, 1996). It was different from the pattern of labeling in the adult, where GAD-IR soma was at higher density in the stratum pyramidale and at the interface between the stratum radiatum and the stratum lacunosum-moleculare. At E21 and P1, GAD67 IHC labeled more prominently processes in the MZs of the hippocampus and dentate gyrus, especially near the cell body layers (Dupuy and Houser, 1996). The preferential location of GABAergic cell bodies at the radiatum-lacunosum moleculare interface started to be observed at P7 by in situ hybridization using probes against both GAD65 and GAD67 (Frahm and Draguhn, 2001). In the dentate gyrus GAD67-positive neurons were first detected in the MZ at E19, and tended to be at higher density near the granule cell layer (Dupuy and Houser, 1996). It was also in contrast with the distribution of GAD67-IR neurons in the mature dentate gyrus, where positive neurons were more numerous in the inner part of the dentate gyrus. This preferential location started to be observed at P7 by in situ hybridization (Frahm and Draguhn, 2001). The neurons containing GAD67 mRNA were located mainly above the granule cell layer at E20, within this layer at P3–P5 and at its bottom at P15 (Dupuy and Houser, 1997; Fig. 6). Since this redistribution was observed for cells labeled by BrdU injection on E14 (i.e., at the birthdate of many of the mature interneurons in the dentate gyrus), and was not accompanied by an important apoptotic cell death, it likely reflects a local migration of interneurons.

A similar translocation of cell bodies was observed for CCK-IR interneurons (Morozov and Freund, 2003). Between P0 and P12, they change from a localization in the molecular layer of the dentate gyrus to their final destination at the granule cell layer/hilus border. They first adopt a horizontal bipolar shape within the molecular layer, then a transitional triangular form, followed by a vertical bipolar form while traversing the granular layer, to finally assume their adult-like pyramidal shape when entering the hilus (Morozov et al., 2006; Fig. 6). These migrating neurons establish immature synapses already at P0, and receive synaptic contacts at P2. In the CA subfields, CCK-IR neurons are first localized in the strata oriens and radiatum, and then concentrate in the distal third of stratum radiatum (Morozov and Freund, 2003). Interestingly, the cell bodies of these interneurons seem to migrate toward their adult location in parallel with a rearrangement of their axonal projections and the acquisition of mature postsynaptic responses to GABA (see later sections). The migration of neurons connected by synapses represents a novel mode of cell movement.

MATURATION OF HIPPOCAMPAL INTERNEURONS

Axonal and Dendritic Arbors

Unlike pyramidal neurons, GABAergic interneurons do not exhibit a stereotyped pattern of dendritic arborization (Freund and Buzsaki, 1996). Furthermore, their axonal arbors vary greatly depending on which parts of the pyramidal neuron they

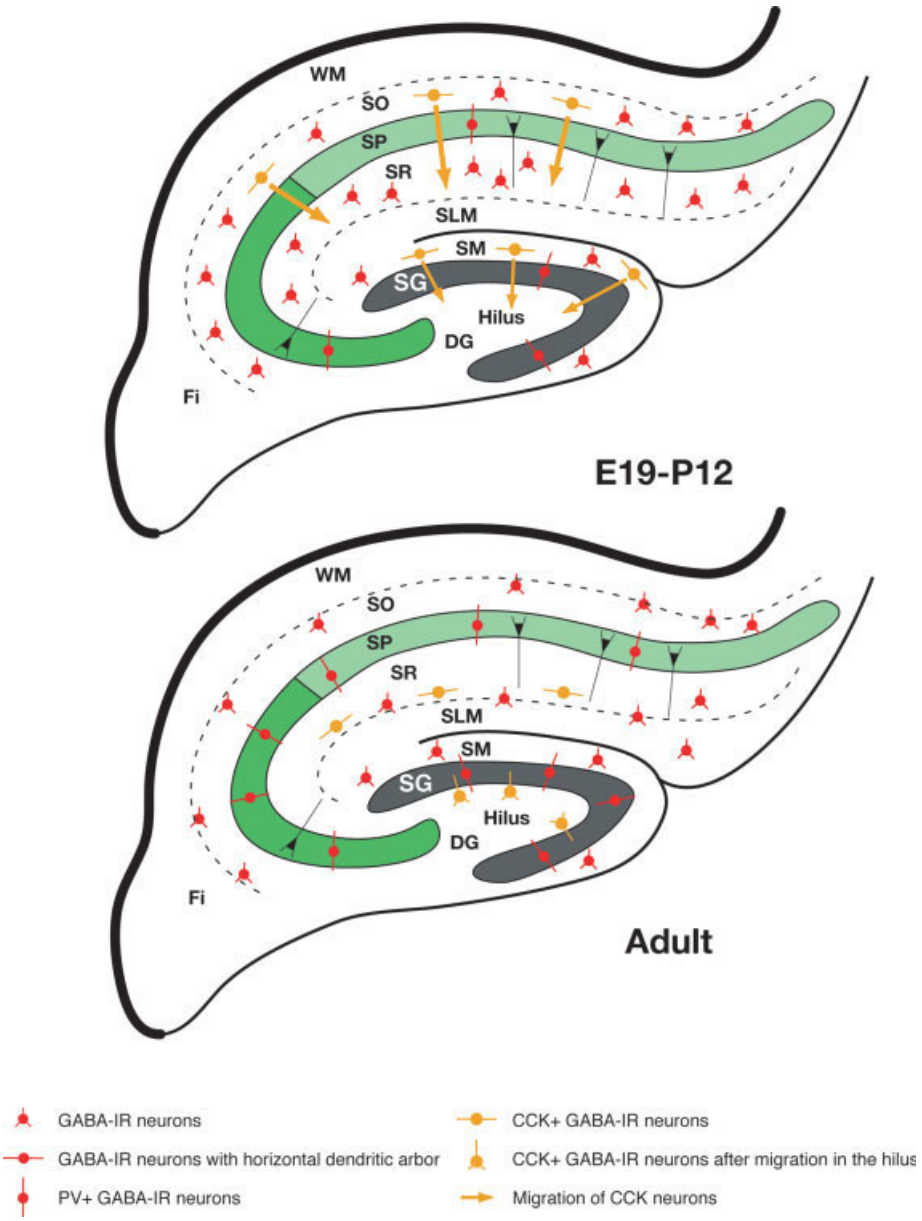

FIGURE 6. Postnatal rearranging of hippocampal gabaergic interneurons. A redistribution of GABAergic soma is observed between birth and adult stage. At perinatal stage, most of GABAergic neurons are in hippocampal marginal zone and subplate (futur SR and oriens, respectively) and in the dentate marginal zone (SM), whereas they are found in majority in the principal cell layer or their immediate surrounding in the adult (Dupuy and Houser, 1996, 1997; Frahm and Draguhn, 2001). Since no apoptotic major event has been describes it has been postulated that GABAergic neurons migrate from the dendritic to the cell body layers, and to the SR-SLM border. CCK-IR interneurons have particularly been shown to migrate in the DG from the SM, crossing the SG to finally settle at the boder of the SG and the hilus (orange neurons). Their migration is paralleled by a change of morphology: horizontal bipolar shape > vertical bipolar shape > adult-like pyramidal shape (Morozov and Freund, 2003; Morozov et al., 2006). DG, dentate gyrus; Fi, fimbria; SG, stratum granulosum; SLM, stratum lacunosum-moleculare; SM, stratum moleculare; SO, stratum oriens; SP, stratum pyramidale; SR, stratum radiatum; WM, white matter.

innervate (see above). This heterogeneity complicates the analysis of their morphological development. Nevertheless, the studies devoted to this topic indicate that although hippocampal interneurons are generated prenatally (see above), their morphological maturation largely extends during the postnatal period.

The morphology of interneurons was analyzed at very early stages of postnatal development (Hennou et al., 2002). Interneurons in newborn rat slices were recorded and labeled by intracellular injections of biocytin in the CA1 area. The coupling of morphological and physiological analysis showed that strikingly, neurons at different stages of their morphological maturation exhibited different patterns of synaptic inputs. Thus, interneurons receiving no spontaneous or evoked postsynaptic currents (PSCs; 5% of the injected interneurons)

had very poorly developed dendrites and axons. Interneurons with only GABAergic PSCs (17%) were morphologically more developed than the previous ones although their dendrites were short and their axons usually had no collaterals. Finally, interneurons with GABA and glutamate PSCs (78%) had more developed dendrites and exhibited axonal branching. Interneurons at various stages of development were intermingled in the same hippocampal stratum. These results indicate that functional GABAergic synapses were detected before glutamatergic synapses. Interestingly, some of the interneurons had long-range projections, such as back-projections to the CA3 area, more extensive than in the adult. Thus, two hypotheses could be proposed. Either these axonal collaterals could be pruned later on during postnatal development or the interneurons establishing aberrant axonal projections may die. Indeed, there is a substantial reduction (45%) of the number of GABAergic neurons in the stratum radiatum of the mouse hippocampus between P5 and P15, and at least part of this reduction seems to be attributable to cell death (Super et al., 1998; Jiang et al., 2001). Since there are a substantial reorganization of GABAergic cell bodies and axonal arborizations, as well as the death of some of the interneurons during postnatal development, it is not clear whether the early functional GABAergic synapses are those ensuring inhibition in the adult.

The maturation of the dendrites of interneurons was followed at later developmental stages using Golgi staining (Lang and Frotscher, 1990). The length of dendrites increased between postnatal day 0 (P0) and P5. This growth of dendritic arbors concerned interneurons located in all hippocampal layers, but was more prominent in the CA3 than in the CA1 area. At this stage, growth cones, filopodia, and irregular varicose swellings were observed. Further increase in dendritic length was observed at P10 and P20, indicating a delayed postnatal development.

Several studies analyzed in more details the postnatal maturation of basket cells. These interneurons innervate the cell bodies and proximal dendrites of principal neurons in the adult (see above). The specificity of this innervation allowed an analysis of the maturation of their axonal arborization in addition to that of their dendritic arbor. Similar to other hippocampal interneurons, their dendrites progressively mature between P2 and P16 in the dentate gyrus (Seress and Ribak, 1990). Dendritic growth cones are frequent at P2 and P5, and reduced in number at P10. At P16 the cell body and dendrites of basket cells reached their adult appearance. The axonal arborization of these interneurons also exhibited a protracted postnatal maturation. At early postnatal stages (P2), the axon of basket cells ramified in the immediate vicinity of the neuron from which it emerges, and over the granule cells located at the border of the molecular layer (i.e., the older granule cells). Later on, basket cells progressively contact neurons located more deeply in the granule cell layer. This maturation of GABAergic innervation towards the hilus was not completed at P16, although at this time the axon developed extensive branching inside and above the granule cell layer. The results of this Golgi study were confirmed by an analysis of the morphology of dentate gyrus basket cells labeled by intracellular injections of horseradish peroxidase at P7–P9 (Seay-Lowe and Claiborne, 1992). At these stages dendritic and axonal processes displayed several immature characteristics. The dendrites and cell bodies exhibited spine-like structures, which are no longer present at adult stages. Furthermore, growth cones were observed on few dendritic and axonal processes. In addition, although axon collaterals were observed in the granule cell layer, the plexuses of axonal varicosities around granule cell bodies were not yet formed. Finally, the dendritic and axonal arbors covered a larger territory than in the adult. For instance, axonal collaterals extended in the CA3 and CA1 subfields. In the dentate gyrus itself, many axonal collaterals were located in the molecular layer, and some axonal collaterals were also observed in the hilus. The establishment of transient axonal projections was also observed for basket cells in the CA3 area at P10–P15 (Cesare et al., 1996). In addition to their dense projection in the pyramidal cell layer, these interneurons exhibited axonal branches extending in the strata oriens and radiatum.

A detailed analysis of the development of CCK-IR interneurons showed that these basket cells also establish transient axonal collaterals during development (Morozov and Freund, 2003). At P4, CCK-IR axonal arborizations were equally distributed in strata oriens, pyramidale, and radiatum. Later on at postnatal day 8, the axonal arborizations concentrate in the pyramidal cell layer. Thereafter, the density of axonal arborizations in this layer strongly increases (see below the time course of GABAergic synaptogenesis), and there is a disappearance of thick axonal collaterals in the stratum radiatum.

Other interneurons than basket cells might also establish transient axonal collaterals during development. Interneurons in the CA3 area labeled by intracellular injection of biocytin were found to exhibit an already well-developed dendritic tree at P2–P6 (Gaiarsa et al., 2001). However, half of these interneurons had immature characteristics, with elongated spine-like or filopodial processes on their dendrites and cell bodies. Interestingly, most of the axonal arbors of interneurons were already mainly restricted to specific domains of glutamatergic neurons at the earliest time points examined, but had axonal collaterals crossing several hippocampal strata. Thus, several types of developing interneurons exhibit axonal collaterals that are likely eliminated later in life.

Synaptogenesis

GABAergic synaptogenesis starts early during development of the hippocampus. As mentioned earlier, already at birth the majority of hippocampal interneurons (95%) received PSCs, only GABAergic (17%) or both GABAergic and glutamatergic (Hennou et al., 2002, see earlier). Thus, functional GABAergic synapses are established before glutamatergic ones. Furthermore, interneurons received functional inputs before pyramidal neurons. Indeed at the same age, the vast majority (80%) of pyramidal neurons of the CA1 area have no PSCs (Tyzio et al., 1999). Therefore, interneurons are the source and the targets of the first functional synapses (Gozlan and Ben-Ari, 2003).

Since GABA exerts depolarizing effects up to postnatal day 10, these early GABAergic synapses could provide an important excitatory drive in the developing hippocampus (Ben-Ari et al., 1989; Ben-Ari, 2001; but see also Sipila et al., 2005).

GABAergic synaptogenesis was studied mainly in the cell body layers. It is likely due to the fact that cell bodies are contacted exclusively by GABAergic terminals (Megías et al., 2001), which facilitates the quantification of synapse number. Despite the early occurrence of the first GABAergic synapses, synaptogenesis by basket cells in the principal cell layers strongly increases at later developmental stages. At P5 in both the dentate gyrus and the CA1 area, basket cells establish immature synapses with cell bodies, characterized by a small size and few synaptic vesicles (Seress et al., 1989). The numbers of GABA-IR neurons and of GABA-IR processes around pyramidal cell bodies strongly increase during the first three postnatal weeks (Seress and Ribak, 1988; Rozenberg et al., 1989). In the dentate gyrus, electron microscopic observations on synapse formation by basket cells correlate well with the light microscopic analysis of the development of their axonal arbors (Seress and Ribak, 1990, see above). The first symmetric (GABAergic) axosomatic synapses of granule cells form at the border of the molecular layer, where the more mature granule cells are located. At this location the number of axosomatic synapses strongly increases during the first 10 postnatal days. In contrast, at the hilar border, the number of symmetric axosomatic synapses increases only after 2 postnatal weeks. In the hippocampus proper, the development of axosomatic terminals was studied after immunostaining with antibodies against the Vesicular Inhibitory Amino Acid Transporter (VIAAT), which label GABAergic terminals (Dumoulin et al., 1999). At P7, VIAAT-IR terminals in the stratum pyramidale were more numerous in the CA3 than in the CA1 area (Marty et al., 2002). In both areas, the number of IR terminals strongly increases (4–6 times) between P7 and P21 (Fig. 7A). Electron microscopic analysis of axo-somatic synapses in the CA3 area correlated well with the light microscopic data, with a strong increase in synapse number between P7 and P21. These observations are in agreement with electrophysiological analyses (Cohen et al., 2000), and indicate a protracted development of axosomatic GABAergic synapses during the postnatal period. Basket cells establish synapses also with the proximal dendrites of principal neurons, and these axo-dendritic synapses are formed together with the axo-somatic synapses at P10 and P16 (Seress and Ribak, 1990). A quantitative analysis of synaptogenesis by other interneuron subtypes targeting pyramidal cell dendrites remains to be performed. Indeed, synaptogenesis in the dendritic layers seem to occur before that in the stratum pyramidale (Tyzio et al., 1999). It might be due to the earlier genesis of interneurons targeting pyramidal cell dendrites (see above).

These studies indicate that interneurons from the dentate gyrus and Ammon's horn progressively acquire mature morphological characteristics during postnatal development. Their dendritic trees loose terminal growth cones in parallel with an elongation of dendritic branches during the first 3 postnatal weeks. The cell bodies and dendrites of interneurons transiently exhibit spines during the first and second postnatal weeks. At this stage, several different types of interneurons have axonal collaterals more widely distributed than in the adult. These axonal collaterals are then likely eliminated, and the axonal arborizations in the principal cell layers increase in density with the establishment of synapses.

Development of Neurochemical Characteristics

The activity of GAD, and the number of GAD- or GABA-IR neurons increase during the second or third postnatal weeks (Seress and Ribak, 1988; Rozenberg et al., 1989; Swann et al., 1989). The two isoforms of GAD display distinct intracellular localizations in the adult, GAD67 being concentrated in cell bodies and GAD65 in presynaptic terminals (Esclapez et al., 1994). During both in vivo and in vitro development, GAD65 immunoreactivity shifted from a labeling of the cell bodies to a more prominent labeling of axonal processes and varicosities (Benson and Cohen, 1996; Dupuy and Houser, 1996; Danglot et al., 2003). The expression of various calcium-binding proteins or neuropeptides also reaches mature levels during the postnatal period (Fig. 8).

Calcium-binding proteins

Neurons containing the calcium-binding proteins PV, CR, and CB represent largely nonoverlapping subpopulations of GABAergic cells in the adult hippocampus (Freund and Buzsaki, 1996; Fig. 2). Unlike PV, which labels basket and axo-axonic interneurons, CB is present in both interneurons and principal cells (granule cells and some pyramidal neurons of CA1). CR-positive neurons can be divided into spiny and aspiny neurons, which innervate respectively the dendrites of principal cells and other GABAergic interneurons.

PV displays a striking pattern of postnatal maturation (Fig. 8). PV immunoreactivity appeared at P4–P7, and PV-IR neurons were faintly labeled at this stage (Nitsch et al., 1990; Seto-Ohshima et al., 1990; Bergmann et al., 1991; Solbach and Celio, 1991). PV immunoreactivity was first detectable in CA3, which matures earlier than CA1 also with respect to the morphology of interneurons and GABAergic synaptogenesis (see above). Consistent with the developmental pattern of PV immunoreactivity, PV mRNA progressively increased during the second and third postnatal weeks (de Lecea et al., 1995).

After a transient and weak expression at embryonic stages (E15–E17) in the outer MZ (prospective stratum lacunosum-moleculare) and in the subplate, CB was expressed at P2 in numerous neurons located in the stratum oriens and stratum radiatum of the mouse hippocampus, as well as in granule cells of the mouse dentate gyrus (Soriano et al., 1994). The mossy fibers started to show CB immunoreactivity at P5.

The developmental pattern of CR expression is more complicated, and exhibits species differences. Already at E14 in the mouse, CR-IR neurons were observed in the primitive plexiform layer (Soriano et al., 1994). At later stages (E15–E18), IR neurons were observed in the outer MZ of the hippocampus and dentate gyrus, in continuity with similar neurons in the MZ of the neocortex. On the basis of their location, morphol-

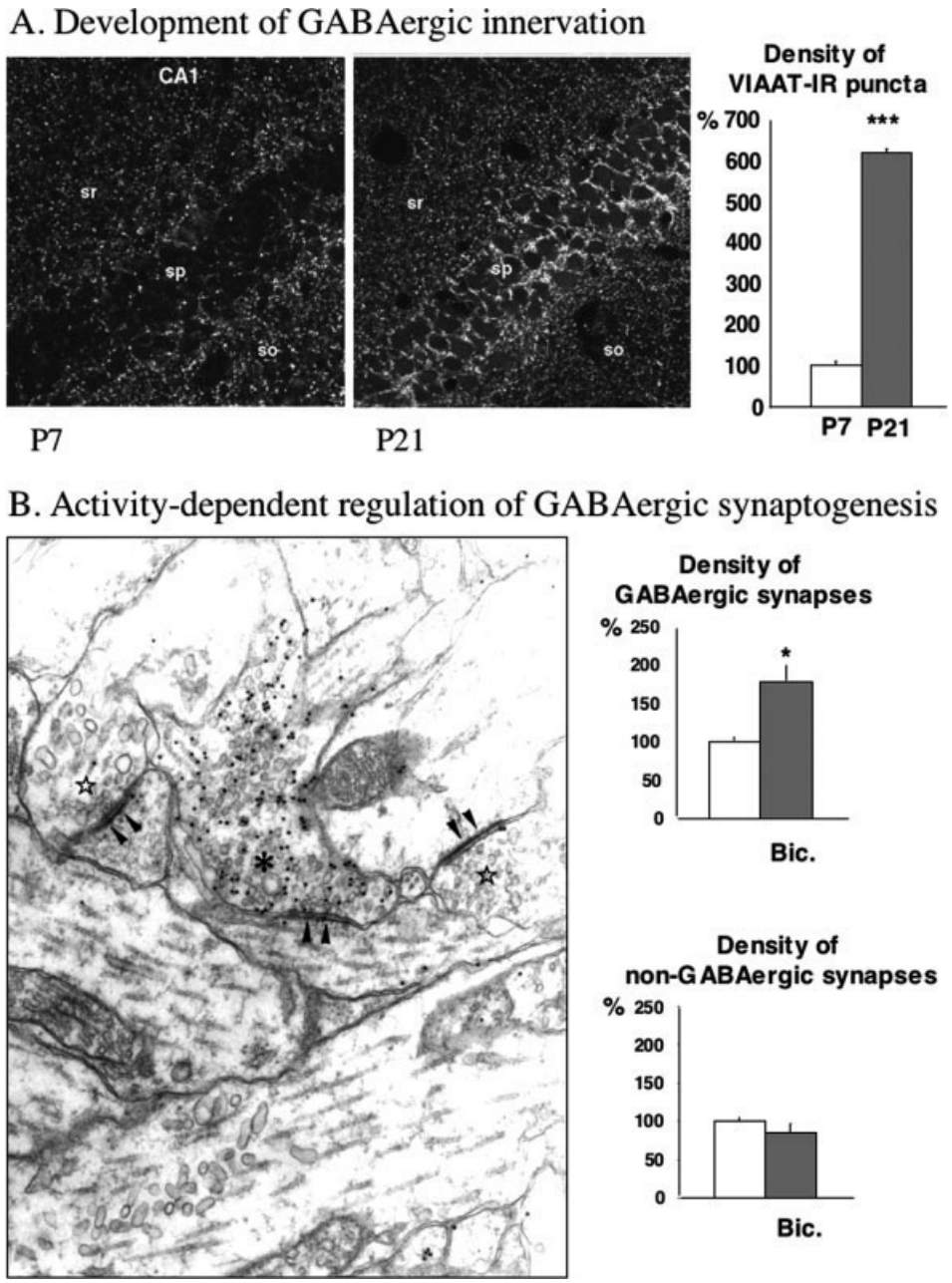

FIGURE 7. Development of GABAergic innervation in the CA1 area. (A) VIAAT immunoreactivity at P7 and P21. The density of VIAAT-IR puncta was quantified in the sp, where a strong increase can be observed between P7 and P21. (B) Effect of a chronic bicuculline treatment on the density of GABAergic and non-GABAergic synapses in hippocampal slice cultures. Slices from P7 rat hippocampus were cultured for two weeks and postembedding immunocytochemistry was performed using antibodies against GABA. Note that the GABAA receptor antagonist bicuculline induces a strong and specific increase in the number of GABAergic synapses, quantified in the so. So, stratum oriens; sp, stratum pyramidale; sr, stratum radiatum. Arrowheads indicate synapses. Stars: non-GABAergic synapses. Asterisk: GABAergic synapse. Modified, with permission, from Marty et al. (2000, 2002). Copyright 2000 by the Society for Neuroscience.

ogy, and CR expression, these neurons can be classified as Cajal-Retzius cells. Immature granule cells were also stained. A different pattern of CR immunostaining was observed during embryonic development of the rat hippocampus (Jiang and Swann, 1997). At E15 labeled neurons were indeed observed in the primitive plexiform layer, but later on a group of monopolar neurons in the subplate and hippocampal plate was labeled instead of Cajal-Retzius cells. These neurons were oriented perpendicularly to the hippocampal plate, and were suggested to be migrating pyramidal cells based on their morphology and location. However, they could also be migrating interneurons, since multipolar CR-IR neurons were observed in the inner MZ. The expression of CR in these neurons is lost during early postnatal development, while Cajal-Retzius cells became labeled. At P10 CR-IR Cajal-Retzius cells were no longer observed. Interneurons were weakly CR-IR at P7–P10. At P15

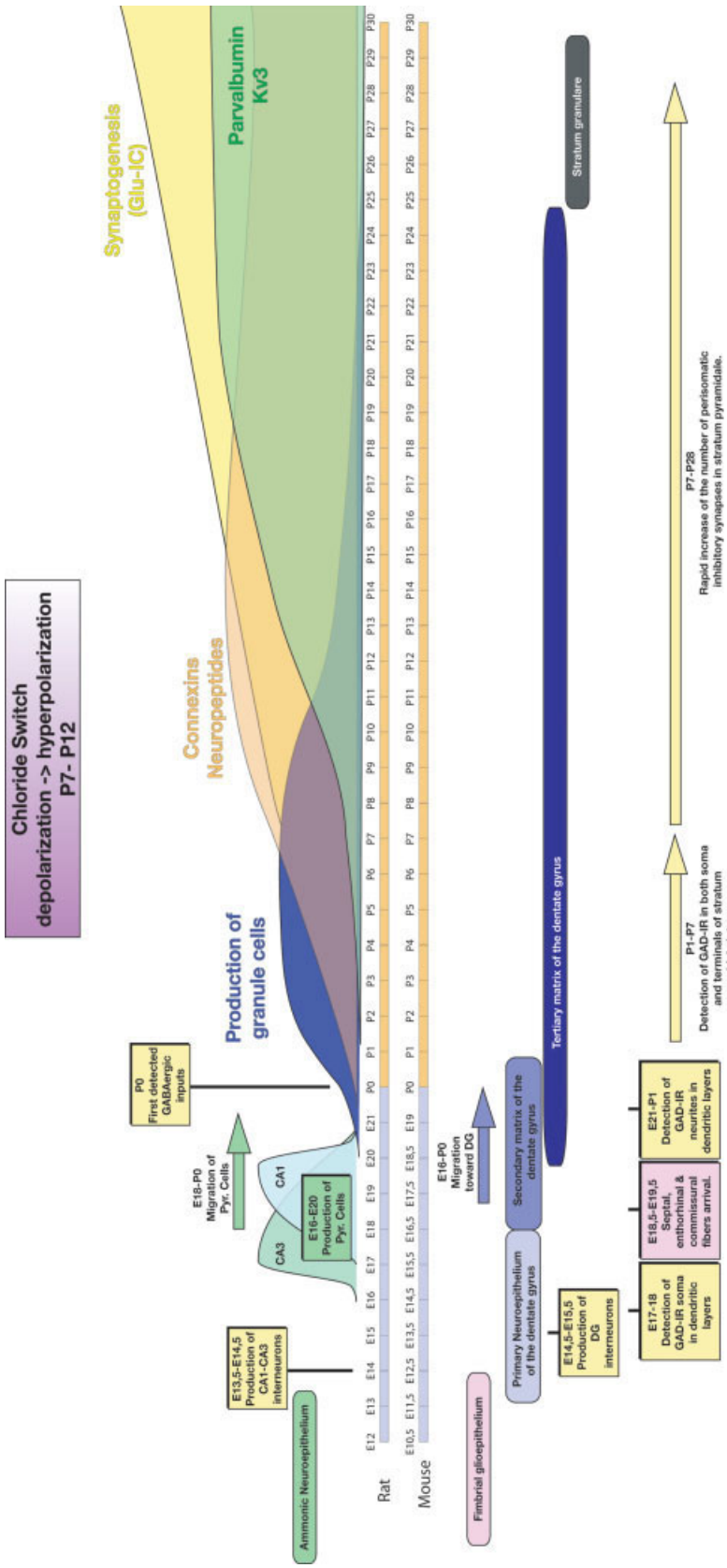

FIGURE 8. Principal events during the development of rat and mouse hippocampal network. The dates indicated in the box concern the rat development. Approximative correspondence between rat and mouse development is shown on the scaled bars. Data concerning the neurogenesis of principal cells are from Altman and Bayer (1990a–c, 1994). Data concerning the neurogenesis of GABAergic interneurons are from Soriano et al. (1989a,b). Data concerning GAD immunoreactivity and the development of synapses are from Rozenberg et al. (1989), Dupuy and Houser (1996), Hennou et al. (2002), and Marty et al. (2002). The time course of glutamatergic synaptogenesis is adapted from Steward and Falk (1991). Data concerning the chloride switch are from Rivera et al. (1999, 2005).

in contrast, they were intensely stained and more numerous than in the adult. Close appositions of dendrites or cell bodies of CR-IR interneurons were also more frequent.

Neuropeptides

Subgroups of hippocampal interneurons are also characterized by the expression of specific neuropeptides such as SOM, CCK, VIP, or neuropeptide Y (NPY; Freund and Buzsaki, 1996). These neuropeptides start to be expressed at late embryonic stages in the hippocampus, but exhibit a dynamic pattern of maturation of their expression during the postnatal period (Fig. 8).

The immunoreactivity for SOM was first detected at E19 in the rat hippocampus, and at P0 in the murine hippocampus (Shiosaka et al., 1982; Soriano et al., 1994). The number of SOM-IR neurons increased up to P10–P15, and then decreased to reach adult values. Interestingly in the hippocampus proper, SOM-IR neurons were confined to the stratum oriens from the earliest time-point of their detection. A parallel maturation was observed for SOM mRNA (Naus et al., 1988). Very similarly, CCK-IR neurons started to be observed at E21, and peaked in number at P10 (Cho et al., 1983), while the level of CCK mRNA peaked at P14 (Takeda et al., 1989). At P0, no VIP-positive cells were observed in the murine hippocampus, while at P5 a few faintly IR neurons were located in the pyramidal cell layer (Soriano et al., 1994). VIP mRNA expression also reached a peak during postnatal development of the hippocampus (Gozes et al., 1987). NPY immunoreactivity, which was first observed at E20 in the rat hippocampus and at E18–P0 in the murine hippocampus, reached adult levels at P21 (Woodhams et al., 1985; Soriano et al., 1994).

These observations indicate that similar to their morphological maturation, hippocampal interneurons acquire their adult neurochemical characteristics during the first 3–4 postnatal weeks, after a peak of expression during the second or third postnatal week.

Voltage-gated potassium channels

PV-IR basket cells exhibit "fast spiking" characteristics that allow their identification during electrophysiological recordings (Kawaguchi et al., 1987). These physiological characteristics are due to the expression of voltage-gated potassium channels of the Kv3 subfamily (Kv3.1 and Kv3.2; Martina et al., 1998). These potassium channels display very similar patterns of expression during development. The Kv3.1b subunit was first detected at P8 and then increased progressively until P40 (Du et al., 1996). It was expressed specifically in PV-IR interneurons, being absent from SOM-IR interneurons. Similarly, the Kv3.2 subunit started to be expressed at P7 and reached full expression at P21 (Tansey et al., 2002). Interestingly, these channels start to be expressed at the same time as PV, at the end of the first postnatal week. It suggests that a coordinated program of gene expression allows the set up of inhibitory transmission by basket cells during postnatal maturation.

Connexin 36

PV-IR interneurons are coupled by gap-junctions in the adult hippocampus (Fukuda and Kosaka, 2000; Venance et al., 2000). Biocytin injections in minislices of the CA3 subfield of P10–P15 rats indicated extensive dye coupling of fast spiking cells (Cesare et al., 1996). It suggested that gap junctions between fast spiking cells could be particularly abundant during postnatal development. A developmental regulation of the electrical coupling of PV-positive interneurons was demonstrated using transgenic animals expressing the Green Fluorescent Protein under the control of the *PV* promoter (Meyer et al., 2002). Both the strength and the incidence of coupling of dentate gyrus basket cells decrease between P14 and P28. Connexin 36 is a major connexin subunit in neurons, and is expressed in hippocampal interneurons (Condorelli et al., 1998; Söhl et al., 1998; Belluardo et al., 2000; Venance et al., 2000). In agreement with the studies on the development of electrical coupling between interneurons, the expression of connexin 36 increases until P7–P16, and then decreases towards adult levels (Söhl et al., 1998; Belluardo et al., 2000).

Maturation of the Postsynaptic Response

During development of the hippocampus, GABA released by interneurons exerts depolarizing effects on the postsynaptic neurons up to postnatal day 10 (Ben-Ari et al., 1989; Ben-Ari, 2001). Additionally, it may exert an inhibitory shunting effect on the activity of pyramidal neurons (Lamsa et al., 2000; Palva et al., 2000). The switch from depolarizing to hyperpolarizing effects of GABA was hypothesized to result from a shift in the equilibrium potential for Cl^-, E_{Cl}, from values more positive than the transmembrane potential (E_m) to values more negative than E_m (Owens et al., 1996). The mature E_{Cl} value is due to expression of the Cl^- extruding, K^+/Cl^- cotransporter KCC2 (Rivera et al., 1999, 2005). Similar to Kv3 potassium channel or PV expression in interneurons, the KCC2 cotransporter starts to be expressed by the postsynaptic targets of interneurons at the end of the first postnatal week. The Na^+, K^+, $2Cl^-$ cotransporter, which accumulates Cl^- in neurons, is expressed earlier but shifts from a somatic to a dendritic localization between P7 and P21 (Marty et al., 2002). Interestingly, modifications of the location of cell bodies and synapses of GABAergic neurons occur in parallel with this maturation of the postsynaptic reponses to GABA (see above). Thus, different GABAergic circuits could subserve the depolarizing effects of GABA during early postnatal development and its mature hyperpolarizing effects.

MECHANISMS OF HIPPOCAMPAL INTERNEURON DEVELOPMENT

Specification of GABAergic Interneurons in the Ganglionic Eminences

Telencephalic progenitors express basic helix–loop–helix domain (bHLH) transcription factors, which specify neuronal

identity by opposition to glial identity. Furthermore, dorsal and basal progenitors express different bHLH transcription factors. Neurogenin 1 and 2 (Ngn 1/2) are specifically expressed by cortical progenitors, whereas Mammalian achaete-scute homolog-1 (Mash1) is expressed by subpallial progenitors. Mutations of *Mash 1* block the differentiation of the LGE and the MGE at an early stage and induce a reduction in the number of cortical GABAergic neurons (Casarosa et al., 1999; Horton et al., 1999). Mash 1 induces the expression of the homeobox genes *Dlx1/2* in the ganglionic eminences (Fode et al., 2000). Expression of the *Dlx* genes induces the production of GABA (Anderson et al., 1999). Moreover, ectopic expression of Dlx2 and 5, but not Dlx1, in cortical neurons induces the expression of GAD (65 and 67) in neurons (Stuhmer et al., 2002). This suggests that *Dlx* genes play a significant role in the specification of telencephalic GABAergic neurons. Later on, when GABAergic interneurons leave the proliferative zone they stop to express Mash1, but continue to express Dlx and GABA (Anderson et al., 1997).

Different transcription factors regulate the specification of the cortex and of the different eminences in the basal telencephalon (for review see Marin and Rubenstein, 2001; Schuurmans and Guillemot, 2002). Dorsal progenitors express Ngn1/2 and the homeodomain transcription factor Pax6 (for review see Rubenstein et al., 1998). In the absence of Ngn or Pax6, cortical progenitors are misspecified, expressing genes typical of ventral telencephal progenitors as if there was a respecification toward ventral neuronal fates (Fode et al., 2000; Yun et al., 2001; Schuurmans et al., 2004). The homeodomain transcription factors Pax6 and Gsh2 have opposing roles in the establishment of the boundary between the cortex and the LGE. Pax6 promotes the generation of the cortical domain, while Gsh2 is involved in the establishment of the LGE domain (Toresson et al., 2000; Yun et al., 2001). The LGE is characterized by the expression of Pax6, whereas the MGE distinctly expresses Nkx2.1 (reviewed in Flames and Marin, 2005). Nkx2.1 is responsible for the generation of the MGE domain (Sussel et al., 1999). Pax 6 and *Nkx2.1* antagonize each other to establish the boundary between LGE and MGE, respectively (Stoykova et al., 2000). Mice lacking the Nkx2.1 homeobox gene exhibit a ventral-to-dorsal transformation in their molecular properties that leads to loss of cell types produced by the MGE and an expansion of cell types produced by LGE (Sussel et al., 1999). To which extent different combinations of transcription factors in the GE could explain the genesis of the various interneuron subtypes remains to be analyzed.

Cues for Migration

Axons can respond to the coordinate action of four types of guidance cues: attractive and repulsive cues, which can be either short or long-range (Tessier-Lavigne and Goodman, 1996). Axons can be guided at short-range by contact-mediated mechanisms involving nondiffusible cell surface and extracellular matrix (ECM) molecules. Long-range guidance cues are diffusible factors secreted by intermediate or final targets that may act over distances of a few hundred micrometers (reviewed in Tessier-Lavigne and Placzeck, 1991). These cues affect growth cone extension and orientation by inhibitory/repulsive or permissive/attractive responses. Three types of signals have been found to direct the migration of GABAergic interneurons: (1) repulsive factors in areas surrounding the GE such as Slits or Semaphorins; (2) motogenic factors in the GE such as HGF, BDNF, and NT4; and (3) permissive or chemoattractive factors in the developping cortex such as Neuregulin-1, GDNF, or the COUP-Tfs (for reviews see Marin and Rubenstein, 2001; Levitt et al., 2004).

Repulsive factors

Chemorepulsive factors produced by preoptic areas prevent interneurons from migrating ventrally and are responsible for their dorsal orientation toward the cortex. Experiments using explant assays suggested that these repulsions are mediated by Slits, which are expressed in the VZ of the LGE (Zhu et al., 1999). However, subcortical repulsion of GABAergic neurons is maintained in Slit1 and Slit2 deficient mice (Marin et al., 2003).

Semaphorins have been suggested to regulate the sorting between striatal and cortical interneurons. Class III Semaphorins (Sema 3A and 3F) are expressed by striatal neurons. Cortical interneurons express Neuropilin 1 (Npn1) and 2 (Npn2), the receptors for semaphorins, which are not expressed by striatal interneurons. Striatal semaphorins exert a chemorepulsive effect on cortical interneurons, thereby creating an exclusion zone and channeling them into adjacent path (Marin et al., 2001). Sema 3A is also expressed in the subplate where it seems to block GE derived neurons expressing Npn1 from entering the cortical plate, guiding them to the dorsal cortex and hippocampus (Tamamaki et al., 2003). Sema 3F expressed in the CP seems to block GE derived neurons expressing Npn2 from entering the CP, prolonging their migration into the lower IZ.

Motogenic factors

Several classes of factors have been shown to promote interneuron migration, including the neurotrophins Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin-4 (NT-4), and Hepatocyte Growth Factor (HGF, also named Scatter Factor, SF). NT-4 is expressed along the migratory path of MGE-derived cells (Polleux et al., 2002). BDNF and NT-4 stimulate tangential migration, whereas inhibition of their receptor TrkB reduces migration. Moreover, *trkB* null mice show a significant decrease in the number of CB-positive cells migrating tangentially in the embryonic cortex. BDNF and NT-4 activate the PI3-kinase in MGE cells and inhibition of this kinase also reduces tangential migration. Altogether these results suggest that TrkB signaling, via PI3-kinase activity, promotes interneuron migration in the developing cortex and hippocampus.

HGF was first described as promoting the proliferation of hepatocytes (Michalopoulos and DeFrances, 1997) and the movement of epithelial cell (hence termed Scatter Factor,

Stoker et al., 1987). HGF is active in pallial and subpallial regions during interneuron migration (Powell et al., 2001). In slice culture, exogenous HGF induces a massive, nondirected movement and a reduction in the number of neurons reaching the cortex. Blocking HGF with antibodies inhibits GE cell motility, suggesting that HGF drives cells to enter a motile state following their exit from the cell cycle (Levitt et al., 2004). HGF needs to be proteolyzed by the serine protease urokinase plasminogen activator (uPA) to be activated. uPA cleaves HGF on its own, but its activity is enhanced when uPA is associated with its GPI-anchored receptor uPAR (for review see Blasi, 1993). Although HGF-deficient mice die at embryonic stage, *uPAR−/−* mice are viable and fertile, and show a decreased HGF activity in the pallium and subpallium. In these mice the number of cortical interneurons is reduced (Powell et al., 2001). The hippocampus of *uPAR−/−* mice shows a loss of GABAergic SOM- but not PV-positive neurons in CA1 and dentate gyrus, suggesting that uPAR is necessary for the normal development of subpopulations of GABAergic neurons in the telencephalon (Eagleson et al., 2005).

GABA released by interneurons could also play a role. GABA acts in vitro as a chemoattractant for cortical neurons (Behar et al., 2001) and inhibition of GABAB receptors results in an accumulation of tangentially migrating neurons in the SVZ (Lopez-Bendito et al., 2003). Interestingly at these early stages, GABA is released in a SNARE-independent mechanism and modulates the migration of hippocampal pyramidal cells (Manent et al., 2005). However, it has been shown recently using organotypic slices from GAD67-GFP knock-in mice that the blockade of GABAA or NMDA receptors fails to modify the migration rate or density of GABAergic interneurons, whereas blockade of AMPA receptors impairs the migration of interneurons (Manent et al., 2006).

The COUP-TFs have also been implied in tangential migration. COUP-TFs are orphan nuclear receptors of the steroid/thyroid family involved in neurogenesis, axogenesis, and neural differentiation (Park et al., 2003). COUP-TFI has previously been proposed to stimulate transcription of vitronectin, an ECM molecule involved in neurite extension (Adam et al., 2000). COUP-TFs are expressed in cells migrating from the basal telencephalon toward the cortex dorsally, and toward the preoptic area and the hypothalamus ventrally (Tripodi et al., 2004). Ectopic expression of the COUP-TFs in the GE increases the rate of migration. COUP-TFI controls both dorsal and ventral migrations, whereas COUP-TFII seems to regulate migration into the IZ of the cortex. It has been proposed that COUP-TFs regulate short and long-range guidance cues (Tripodi et al., 2004).

Attractive factors

The cortex expresses diffusible factors attracting tangentially migrating interneurons (Marin et al., 2003; Wichterle et al., 2003). Areas surrounding the MGE are nonpermissive for MGE cell migration, whereas dorsal regions leading to the cortex are increasingly permissive (Wichterle et al., 2003). The neuregulin receptor erbB4 is preferentially expressed by tangentially migrating interneurons, and this erbB4-positive stream in the lower IZ shifts toward the cortex and the hippocampal primordium (Yau et al., 2003). It suggests that neuregulin/erbB4 signaling might regulate the migration of telencephalic interneurons. Indeed, neuregulin-1 is expressed in the developing cortex and in the route of tangentially migrating neurons, and perturbing erbB4 function decreases the number of interneurons migrating tangentially into the cortex (Flames et al., 2004).

Recently, GDNF and its receptor GFRα1 have been shown to promote the differentiation and tangential migration of cortical GABAergic neurons (Pozas and Ibanez, 2005). They are expressed in the MGE and along the tangential migratory pathway of GABAergic cells in the developing cortex. GDNF acts as a potent chemoattractant for GABAergic cells, and mutant mice for GDNF or GFRa1 showed reduced numbers of GABAergic cells in the cerebral cortex and hippocampus.

Tangentially migrating neurons might also interact with corticofugal axonal fibers in the IZ (O'Rourke et al., 1995; Métin et al., 2000; Poluch et al., 2001). Corticofugal growing axons are in close apposition with CB-positive IZ cells (Métin et al., 2000). The neural cell adhesion molecule TAG-1 (also known as contactin 2), which is expressed in the developing corticofugal system, promotes the migration of cortical interneurons (Denaxa et al., 2001). Blocking the function of TAG-1, but not of L1, another adhesion molecule expressed by thalamocortical axons, results in a marked reduction of the number of GABAergic neurons in the cortex. The authors proposed a model in which MGE cells migrate away from the GE due to the repulsive effect of Slit, and use then TAG-1 expressed by corticofugal axons arranged tangentially in the MZ and IZ to migrate in the cortex. To reach their final position in the CP, interneurons could use radially arranged bundles of efferent axons or radial glial fibers (Denaxa et al., 2001).

The chemokine Stromal cell-derived factor-1 (SDF-1) is highly expressed in the leptomeninges of the embryonic cortex (Stumm et al., 2003). Migrating interneurons express its receptor CXC chemokine receptor 4 (CXCR4). In *SDF-1* or *CXCR4* knock-out mice, interneurons are less numerous in the superficial layers of the neocortex. Thus, SDF-1 may regulate the last steps of interneuron migration.

Signals From the Postsynaptic Neurons Triggering GABAergic Synaptogenesis

At birth, interneurons at different stages of development are intermingled in the same layer (Hennou et al., 2002). However, only the interneurons at a certain degree of morphological maturation receive functional synaptic inputs, first from GABAergic and then from glutamatergic neurons. The same phenomenon is observed for pyramidal neurons, but with a delay (Tyzio et al., 1999). These observations suggest that the degree of maturation of postsynaptic neurons is the limiting factor for the establishment of synapses. They are in agreement with heterochronic coculture experiments, showing that axons are competent to estab-

lish synapses before the postsynaptic somato-dendritic compartment (Fletcher et al., 1994). Several other aspects of GABAergic synaptogenesis in the hippocampus also support this hypothesis. The maturation of GABAergic terminals on CA1 pyramidal cell bodies is delayed when compared with that on CA3 pyramidal neurons, which are generated earlier (Altman and Bayer, 1990b; Marty et al., 2002). In the granule cell layer, basket cells establish their first synapses with the more mature dentate granule cells, at the border of the molecular layer (Seress and Ribak, 1990). These results suggest that neurons reaching a certain stage of their development start to express molecules triggering synaptogenesis with nearby GABAergic axons.

The identity of the signals emitted by the postsynaptic neurons and triggering GABAergic synaptogenesis remain unknown. Recent studies point neuroligin-2 as a potential postsynaptic inducer of GABAergic synaptogenesis. Indeed, it is specifically expressed at GABAergic synapses (Graf et al., 2004; Varoqueaux et al., 2004). In immature neurons, it colocalizes with aggregates of GABAA receptors not facing presynaptic terminals (Varoqueaux et al., 2004). Finally, neuroligin-2 overexpression increases the number of GABAergic terminals (Chih et al., 2005; Levinson et al., 2005). Knock-out experiments would be required to further test this hypothesis.

In addition to a signal triggering GABAergic synaptogenesis, the postsynaptic neuron must also emit signals for its different compartments, i.e., axon initial segment, cell body, and different layers on the dendritic arbor, to achieve the specificity of GABAergic synaptogenesis. This signaling does not seem to depend on extra- or even intrahippocampal afferents, as PV-IR innervation of pyramidal cell bodies developed in organotypic slice cultures of isolated CA3 area from P1 rat hippocampus (Marty, 2000). The segregation of terminals from basket and bitufted interneurons on, respectively, the soma and dendrites of pyramidal neurons also develop in organotypic slice cultures of the primary visual cortex (Di Cristo et al., 2004). A preferential targeting of GABAergic vs. non-GABAergic terminals on the somata of pyramidal neurons is even observed in dissociated cell cultures (Benson and Cohen, 1996). Furthermore, this preferential targeting is maintained in the presence of tetrodotoxin, indicating that it is independent of spiking activity. In Purkinje neurons, the membrane adaptor protein ankyrinG allows the localization of neurofascin186, an L1 cell adhesion molecule, at the axon initial segment (Ango et al., 2004). The subcellular gradient of neurofascin186 in turn directs the formation of "pinceau synapses" by basket cells on the axon initial segment of Purkinje cells.

Cell adhesion molecules also promote perisomatic inhibitory synaptogenesis in the hippocampus. Mice deficient for the neural cell adhesion molecule L1 exhibit a reduction of the density of perisomatic active zones, together with a reduction of the frequency of miniature inhibitory PSCs (Saghatelyan et al., 2004). N-Cadherin might also play a role during GABAergic synaptogenesis, as it is transiently expressed at GABAergic synapses in hippocampal cultures (Benson and Tanaka, 1998).

Similarly, molecules of the ECM are involved in regulating the number of axo-somatic synapses. Tenascin-R (TN-R) is a member of the tenascin family predominantly expressed in the central nervous system (Dityatev and Schachner, 2003). It plays a role in the formation of perineuronal nets, which are structures enriched in ECM molecules located around PV-IR cell bodies and proximal dendrites (Celio et al., 1998; Weber et al., 1999; Bruckner et al., 2000). The HNK-1 carbohydrate, likely carried by TN-R, is also present at GABAergic terminals around pyramidal cell bodies (Saghatelyan et al., 2000). TN-R-deficient mice have a reduction in number and size of symmetric perisomatic synapses in the CA1 area (Nikonenko et al., 2003).

The molecular determinants of GABAergic synaptogenesis remain largely unknown. The specific innervation of subdomains of pyramidal neurons by the various interneurons suggests the existence of distinct cues on each of these subdomains. Thus, if the time and location of interneuron genesis in the GE determine their identity, they should also induce the expression of molecules allowing their axons to recognize particular cues on the pyramidal neurons.

Neuronal Activity Promotes Dendritogenesis, Synaptogenesis, and Neuropeptide Expression by Interneurons

The number of excitatory, asymmetric synapses in the hippocampus strongly increases during the first postnatal month (Steward and Falk, 1991). This increase occurs in parallel with the maturation of the morphological and neurochemical characteristics of interneurons (see above). It suggests that neuronal activity could promote synaptogenesis, dendritogenesis, or neuropeptide synthesis by hippocampal interneurons. Studies in several other brain areas support this hypothesis. In their classical studies, Hendry and Jones demonstrated the activity-dependent regulation of GABA immunoreactivity in the visual cortex of adult monkeys (Hendry and Jones, 1986; Jones et al., 1994a). More recently, an activity-dependent regulation of the number of perisomatic GABAergic synapses was observed in cultures of postnatal cerebellar or visual cortex slices (Chattopadhyaya et al., 2004; Seil and Drake-Baumann, 1994). Furthermore, activity-dependent regulations of perisomatic GABAergic synapses in the developing visual cortex, and of GABAergic synapses on dendritic spines in the developing and adult barrel cortex, were also observed in vivo (Micheva and Beaulieu, 1995; Knott et al., 2002; Chattopadhyaya et al., 2004). Neuronal activity was also found to increase the dendritic arborization and the expression of NPY, GAD, or PV by neocortical interneurons in organotypic slice cultures (Wirth et al., 1998; Jin et al., 2003; Patz et al., 2003, 2004).

Several studies indicate that neuronal activity promotes the morphological and neurochemical maturation of hippocampal interneurons in vitro. Thus, depolarizing stimuli increase the dendritic arborization of GABAergic neurons in dissociated cultures of embryonic neurons (Marty et al., 1996a; Berghuis et al., 2004). Furthermore, neuronal activity promotes GABAergic synaptogenesis in slices from P0 or P7 hippocampus (Marty et al., 2000, 2004; Colin-Le Brun et al., 2004; Fig. 7B). At early developmental stages, the depolarizing action of GABA was involved in these effects of activity on the morpho-

logical maturation of interneurons (Marty et al., 1996a; Colin-Le Brun et al., 2004; Represa and Ben-Ari, 2005). An activity-dependent regulation of neuropeptide Y and SOM, but not of PV, was also observed in hippocampal slice cultures (Marty et al., 1996b, Marty and Onteniente, 1997; Marty, 2000). Thus, the peak of expression of neuropeptides during postnatal development could be explained by the transient hyperexcitability of hippocampal circuits during this period (Gomez-Di Cesare et al., 1997). This regulation of neuropeptide levels by neuronal activity is conserved in the adult hippocampus, as observed after seizures (Gall et al., 1990; Schwarzer et al., 1996). Noticeably, even a strong up-regulation of the neuropeptides SOM or neuropeptide Y in slices at P7 did not induce ectopic expression in other types of interneurons (Marty and Onteniente, 1997, 1999). It suggests that at these developmental stages, neuronal activity controls the level of expression of neuropeptides in groups of interneurons already committed to express particular neurochemical characteristics (see above).

BDNF as a Mediator of the Effects of Neuronal Activity

Neurotrophic factors may be a link in the chain by which neuronal activity controls the development of hippocampal interneurons. Particularly, the members of the neurotrophin family BDNF, neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5) promote the morphological and neurochemical maturation of hippocampal or neocortical interneurons (Marty et al., 1997). Thus, Nawa and collaborators have shown important effects of BDNF on neuropeptide expression, in dissociated cultures or following in vivo infusions in developing or adult brains (Nawa et al., 1993, 1994; Croll et al., 1994; Carnahan and Nawa, 1995). Accordingly, the levels of NPY and of various calcium-binding proteins were reduced in interneurons of BDNF knock-out mice (Jones et al., 1994b). Since both the synthesis and the release of BDNF are dependent on neuronal activity (Thoenen, 1995), it was proposed that BDNF could mediate the effects of neuronal activity on neuropeptide expression (Carnahan and Nawa, 1995; Nawa et al., 1995). In agreement, the increase in NPY expression after seizure activity in the adult hippocampus was preceded by an important rise in BDNF protein level (Nawa et al., 1995). Indeed, the increased NPY immunoreactivity triggered by depolarizing stimulation was abolished in cultures from BDNF-deficient mice (Marty et al., 1996a). BDNF also selectively increased the amplitude of AMPA-mediated miniature excitatory PSCs and the synthesis of AMPA receptors in interneurons (Rutherford et al., 1998; Nagano et al., 2003). BDNF increased the size of neocortical neurons in dissociated cultures, and promoted the elongation of the dendrites of hippocampal interneurons in slice cultures (Marty et al., 1996a; Yamada et al., 2002; Kohara et al., 2003; Berghuis et al., 2004). Using organotypic slice culture, it was shown that the activity-dependent dendritic growth of neocortical interneurons was also mediated by BDNF (Jin et al., 2003). Finally, BDNF also promoted GABAergic synaptogenesis. BDNF increased the formation of functional inhibitory synapses in cell cultures (Rutherford et al., 1997; Vicario-Abejon et al., 1998; McLean Bolton et al., 2000; Palizvan et al., 2004; Ohba et al., 2005). In vivo, BDNF overexpression accelerated the maturation of GABAergic synaptogenesis in the visual cortex (Huang et al., 1999). The role of the endogenous BDNF in the establishment of GABAergic synaptogenesis in vivo was demonstrated in the cerebellum using conditional knock-out of the BDNF receptor TrkB (Rico et al., 2002). The effects of neuronal activity on GABAergic synaptogenesis were also mediated, at least partially, by BDNF. In cerebellar or hippocampal slice cultures, antibodies against BDNF and NT-4/5 prevented or reduced the activity-dependent GABAergic synaptogenesis (Marty et al., 2000; Seil and Drake-Baumann, 2000). Hippocampal interneurons express TrkB but not BDNF itself, which is synthesized by pyramidal neurons (Altar et al., 1994; Rocamora et al., 1996; Schmidt-Kastner et al., 1996; Zachrisson et al., 1996). Thus, BDNF could act as a target-derived trophic factor to promote the maturation of interneurons as a function of the activity of pyramidal neurons.

CONCLUDING REMARKS

The studies reviewed here indicate that hippocampal interneurons develop through an extended period of time, with the sequential and overlapping acquisition of their various morphological and neurochemical characteristics (Fig. 8). Interplay of intrinsic determinants and extrinsic factors influences this development. The place of birth of interneurons in the ganglionic eminences, and the particular combination of transcription factors expressed by neurons at this location, might determine their main neurochemical characteristics and the connectivity that they will establish after their migration to the hippocampus. The factors responsible for the specificity of the connections established by interneurons remain to be discovered. Although the first GABAergic inputs are detected very early, at late embryonic stages, GABAergic synaptogenesis is a protracted postnatal process. The protracted morphological and neurochemical maturation of interneurons might allow neuronal activity to regulate the number of their dendritic branches and axonal varicosities, and their level of expression of neuropeptides. GABAergic transmission has a crucial role in the elaboration of the complex pattern of network activity (Somogyi and Klausberger, 2005). The role of patterned activity in the maturation of interneurons remains to be studied. Remarkably, and contrary to the primary sensory cortices, neuronal activity in the developing postnatal hippocampus might not be driven by environmental stimulation (Waters et al., 1997). The influential role of neuronal activity could help in establishing appropriate levels of inhibition in face of the developing excitatory connections (Corner and Ramakers, 1992). For instance, regulation of neuropeptide levels during developement could set up appropriate neuroprotective mechanisms. The neuropeptides NPY or SOM inhibit glutamatergic transmission by acting on presynaptic excitatory terminals (McQuiston and Colmers, 1996; Boehm and Betz, 1997). They could be involved in preventing seizure

activity in the adult (Moneta et al., 2002; Richichi et al., 2004). Thus, NPY or SOM knock-out mice are more susceptible to seizures (Baraban et al., 1997; Buckmaster et al., 2002). Such feedback mechanisms would be even more powerful when excitatory activity specifically regulates AMPA receptors expressed on interneurons or GABAergic synaptogenesis. The developing brain is particularly proned to seizure (Gomez-Di Cesare et al., 1997; Swann et al., 2001; Bender et al., 2004; Khazipov et al., 2004). This susceptibility could be partly due to the lag between excitatory synaptogenesis and its positive feedback on inhibitory mechanisms through the promotion of GABAergic synaptogenesis and AMPAR expression by interneurons.

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