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Migration of neurons from their birthplace to their final destination is an extremely important step in brain maturation, and cortical migration disorders are the most common brain developmental alteration observed in human patients. Among the mechanisms that govern neuronal migration, the neurotransmitters GABA and glutamate deserve particular attention: 1) neurotransmitters and receptors are expressed early in the developing brain, 2) neurotransmitters may act as paracrine signaling molecules in the immature brain, and 3) neurotransmitters regulate intracellular calcium required for many cellular functions, including cytoskeletal dynamic changes. Thus, many reports reviewed here aimed to demonstrate that the activation of specific GABA and glutamate receptors is instrumental in cell migration by acting as motility promoting, acceleratory, or stop signal. Interestingly, the regulation of migration by neurotransmitters and receptors depends on the type of migration (radial, tangential, or chain migration), the type of cells (principal glutamatergic neurons vs. GABAergic interneurons), and the brain area (neocortex, cerebellum, rostral migratory stream). A hypothesis is proposed that these differential actions in different cell types arise from a "homeostatic-like" regulation that controls final position, timing, and number of cells at destination. NEUROSCIENTIST 13(3):268–279, 2007. DOI: 10.1177/1073858406298918

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Development of the human brain proceeds through two main stages, the first involving neuronal proliferation and migration and the second leading to morpho-functional organization and synaptogenesis. The first stage occurs between mainly the second and fifth month of gestation in humans and embryonic days (E) 12 and 18 in small rodents (rat and mice) (Bayer and others 1993). The second stage is long lasting and occurs in humans from the fifth gestational month and mainly after birth in small rodents (Avishai-Eliner and others 2002).

Numerous mechanisms coordinate these stages to produce the appropriate number and types of neurons distributed within the appropriate layers and fields and then to form equilibrated excitatory and inhibitory networks.

During the past years, a fruitful debate has challenged the contribution of genetic and environmental factors to brain construction and pathology. There is a general consensus that infectious agents, drugs, and hormones, among other physicochemical factors, may perturb brain development (Gressens and others 2001). More interestingly, different data support the notion that factors modulating brain activity, acting mainly through receptors for neurotransmitters, are instrumental for brain construction. This type of action was first proposed to be involved in synaptic plasticity, and it is generally assumed that neuronal activity plays a major role in sculpting neuronal networks. More recently, neurotransmitters have been found to act on the immature brain as paracrine factors that may be released to the extracellular space and diffuse relatively long distances to activate maturing neurons, including migrating neurons (Demarque and others 2002; Manent and others 2005). To some extent, neurotransmitters play the role of chemical messengers between neurons, even in the absence of any synaptic input. What is the role of the paracrine action of neurotransmitters in the maturing brain? In this review, we summarize data published mainly during the past decade, showing that paracrine neurotransmitters—namely, glutamate and GABA—modulate neuronal migration. Neurotransmitters have a differential affect, depending on the neuronal cell type (principal cells or interneurons), the brain area (neocortex, hippocampus, olfactory bulb, or cerebellum), and the mode of migration (radial, tangential, chain migration). We also consider whether the role of neurotransmitters in migration shows a bidirectional communication between future GABAergic and glutamatergic synaptic partners. Recent data from our lab support a model

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of homeostatic developmental mechanisms that serve to construct a cortical field containing the appropriate number of excitatory and inhibitory neurons (Manent and others 2006).

Distinct Modes of Neuronal Migration

Subunits of ionotropic GABA and glutamate receptors are detected early during development, being expressed by various cell types of the developing brain, including progenitors, migrating neurons, immature neurons, and glia. In addition, GABA and glutamate are detected early within the neuronal micro-environment of the developing brain. Early actions of these transmitters are thus possible, influencing every stage of the brain construction, from cell cycle exit to migration and differentiation (Nguyen and others 2001). The following section focuses on the actions of GABA and glutamate during neuronal migration.

Distinct neuronal subtypes use distinct migratory modalities to reach their final destinations. Three distinct modes of migration can be distinguished: 1) a radial mode of migration for excitatory neurons, referred to as *radial migration;* 2) a tangential mode of migration for interneurons, referred to as *tangential migration;* and 3) a mode of migration as neuronal chains for neurons of the olfactory bulb, referred to as *rostral migration*. Each mode of migration, as well as its specific modulation by the transmitters GABA and glutamate, is described.

Radial Migration

Principal Cells of the Neocortex

Once generated at the level of the germinal layers lining the ventricular system, pioneer cortical neuroblasts migrate radially to form the first identifiable cortical layer, the preplate. The subsequently generated neuroblasts migrate within the preplate and form the cortical plate (CP), dividing the preplate into a superficial layer, the marginal zone (MZ), and a deep layer, the subplate (SP). Once the CP is formed, succeeding waves of newly generated neurons migrate in an inside-to-outside fashion, such that early generated neurons settle into the deepest layers, and late-generated neurons migrate past the existing layers to form the most superficial layers. During the CP stage, neurons migrate radially along radial glial fibers and display the canonical features of migrating neurons described by Rakic (1972) in his early electron-microscopic studies. These migrating neuroblasts have a bipolar morphology, with a leading process directed toward the direction of migration and a trailing process oriented in the opposite direction. A more precise view of cortical cell migration has emerged from lineage analyses using retroviral constructs coding for the green fluorescent protein (GFP). From these experiments (Noctor and others 2004; Tabata and Nakajima 2003), neuronal migration at the CP stage can be divided into 4 distinct phases: 1) rapid movement to the subventricular zone (SVZ), 2) prolonged sojourn in the SVZ (this stage is also referred to as the multipolar stage, in which neurons migrate in a multipolar manner, extending multiple dynamic processes), 3) retrograde migration toward the ventricle, and 4) radial, glial-guided migration throughout the intermediate zone (IZ) to the target layer. This latter stage corresponds to the classical model of radial migration described by Rakic.

Migrating pyramidal neurons are influenced by GABA and glutamate along their journey to their target layers. Chemotropic actions of GABA were first identified using chemotaxis chambers, where dissociated cortical cells were allowed to undergo gradient-dependent migration (Behar and others 1996) but have been refined using organotypic neocortical explants incubated with antagonists of GABA receptors. In these preparations, GABA acting through picrotoxin-sensitive $GABA_{A/C}$ receptors promoted the cortical entry of migrating neuroblasts, leaving the germinal zones (ventricular zone [VZ]/SVZ) to migrate throughout the IZ. GABA acting through saclofen-sensitive $GABA_B$ receptors promotes the entry of migrating neuroblasts from the IZ to the CP, where the activation of $GABA_A$ receptors provides a stop signal to end migration (Behar and others 2000; see Fig. 1). $GABA_A$ receptors responsible for this stop signal desensitize, and their overactivation by the agonist muscimol, in vivo or in vitro, causes heterotopias in the most superficial cortical layers, probably because of an overmigration due to a loss of the stop signal (Heck and others 2007).

Modulatory actions of glutamate have also been identified using chemotaxis chambers. In these preparations, glutamate acting on *N*-methyl-D-aspartate (NMDA) receptors, but not on other ionotropic glutamate receptors, induces the motility of cells dissociated from the cortical germinal zones (Behar and others 1999). These results have been confirmed using organotypic neocortical explants, where the incubation with 2 antagonists of NMDA receptors, APV and MK801, impaired the migration of young cortical neurons (Behar and others 1999; Hirai and others 1999; see Fig. 1). Similarly to $GABA_A$ receptor overactivation, overactivation of NMDA receptors by ibotenate injected in vivo (Marret and others 1996) or applied to slices (Kihara and others 2002) also induces migration defects.

Principal Cells of the Hippocampus

The hippocampus is a simplified cortical structure composed of a reduced number of neuronal layers relative to the neocortex. Principal cells are densely packed into a single cellular layer, the pyramidal cell layer. As in the developing neocortex, successive waves of pyramidal neurons are generated from the germinal neuroepithelium, and neurons migrate in an inside-to-outside fashion so that cells located in the deepest part of the pyramidal cell layer (i.e., close to the stratum oriens) are generated before cells located in the most superficial part (i.e., close to the stratum radiatum) (Altman and Bayer 1990; Manent and others 2005). A more precise description of the modes of migration used by young pyramidal cells has emerged from experiments using in utero electroporations with plasmids encoding GFP (Nakahira and Yuasa 2005). According to these experiments, pyramidal neurons of the CA1 region migrate in a multipolar fashion at the earliest stages and then shift to a glial-guided mode of migration;

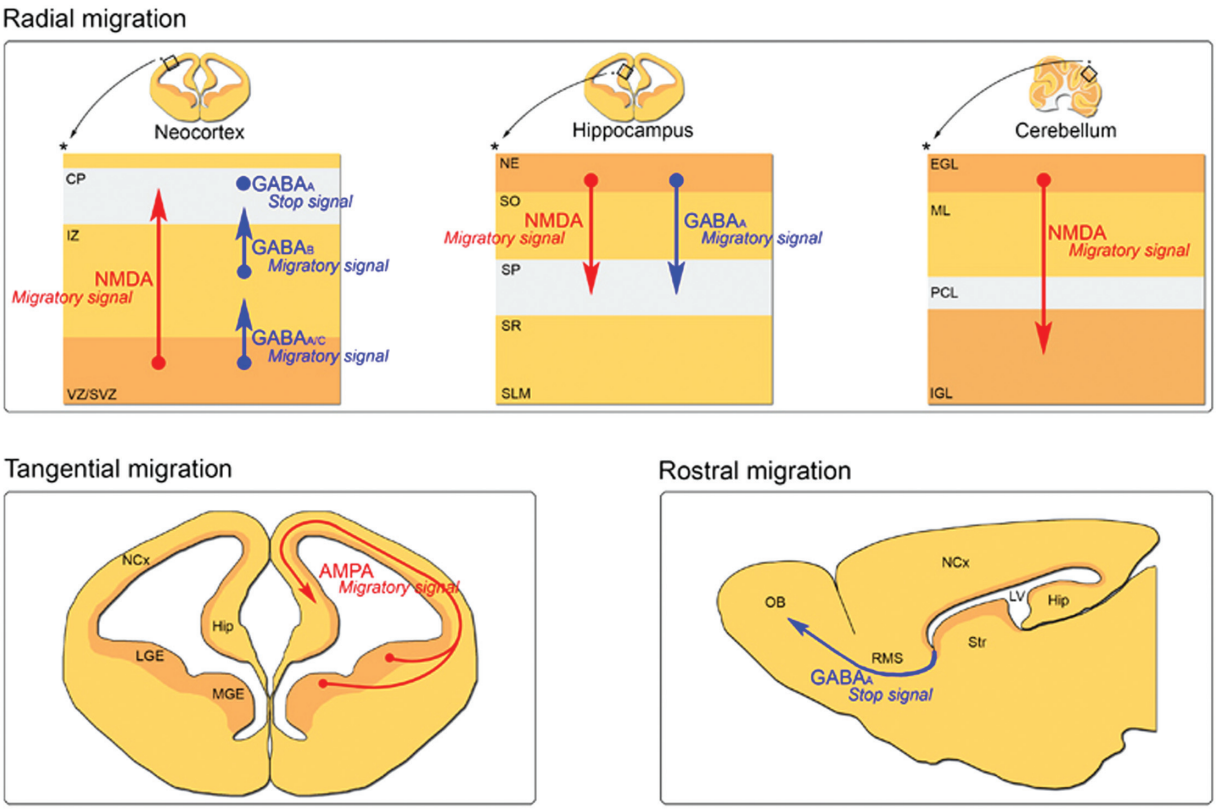

Fig. 1. Modes of neuronal migration and their respective modulations by GABA and glutamate, as a function of the brain structures considered. For each migratory modality and brain structure, glutamate receptor-mediated modulations of neuronal migration are symbolized with red arrows, whereas GABA receptor-mediated modulations are symbolized with blue arrows. Receptor subtypes implicated in the modulation are indicated, as well as the types of modulatory actions. NMDA, *N*-methyl-D-aspartate; CP, cortical plate; IZ, intermediate zone; VZ/SVZ, ventricular zone/subventricular zone; NE, neuroepithelium; SO, stratum oriens; SP, stratum pyramidale; SR, stratum radiatum; SLM, stratum lacunosum moleculare; EGL, external granular layer; ML, molecular layer; PCL, Purkinje cell layer; IGL, internal granular layer; NCx, neocortex; Hip, hippocampus; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; OB, olfactory bulb; RMS, rostral migratory stream; Str, striatum; LV, lateral ventricle.

this latter mode is comparable to that used by principal cells of the neocortex at later stages.

Modulatory actions of GABA and glutamate during CA1 hippocampal pyramidal cell migration at later stages have been investigated recently. Electrophysiological recordings of fluorescent neuroblasts migrating in organotypic slice cultures have revealed that these cells express functional $GABA_A$ and NMDA receptors but not AMPA/kainate (KA) receptors (Manent and others 2005). Incubation with antagonists of $GABA_A$ and NMDA receptors, but not AMPA/KA receptors, perturbed migration of these cells (see Fig. 1), shortened their leading processes, and strongly reduced the number of cells reaching their target (Manent and others 2005; Fig. 2). Moreover, the effects of antagonists were still observed in slices prepared from mutant mice defective in soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)–dependent vesicular release of transmitters. These results suggest that a nonconventional release of GABA and glutamate modulates neuronal migration, in keeping with the recent observation of a paracrine mode of communication through those transmitters prior to synapse formation (see below and Demarque and others 2002).

Cerebellar Granule Cells

Cerebellar granule cell migration has been extensively described (for a review, see Komuro and Kumada 2005). In brief, postmitotic granule cells in the upper strata of the external granular layer (EGL) initially migrate tangentially and then extend a vertical process along Bergman glia fibers and migrate radially along glial fibers through the molecular layer (ML). Migrating granule cells in the ML display features typical of migrating neurons: elongated soma, a leading process directed toward the direction of movement, and a thin trailing process oriented in the opposite direction. Granule cells migrate through the ML in a saltatory manner, alternating pauses with forward or backward movements, and remain stationary when reaching the Purkinje cell layer (PCL), retracting their leading

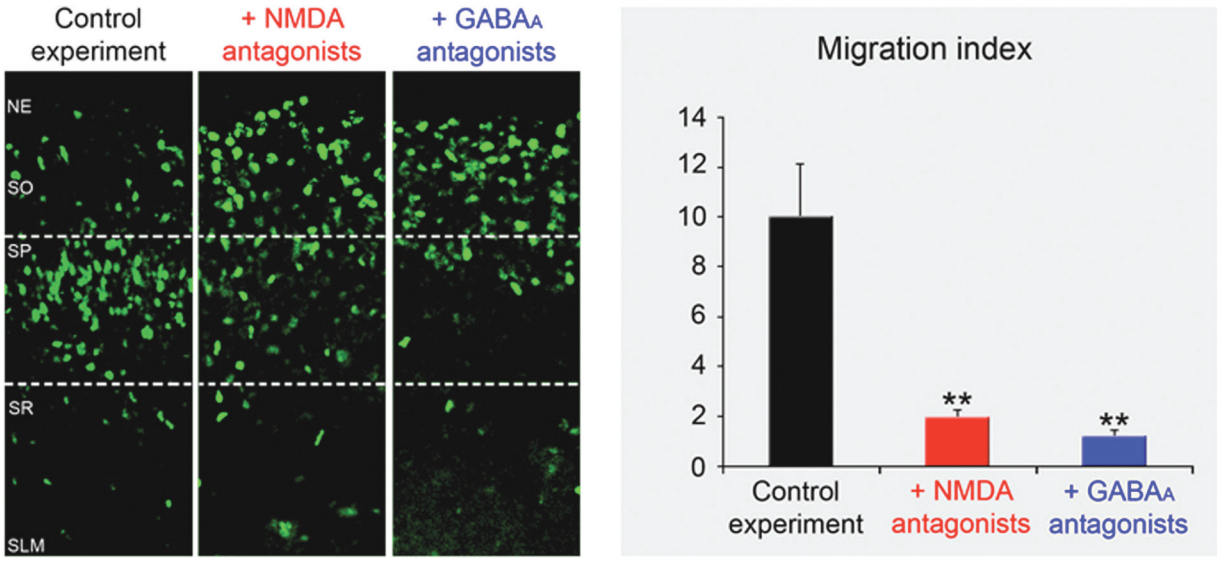

Fig. 2. $GABA_A$ and *N*-methyl-D-aspartate (NMDA) receptor antagonists prevent hippocampal pyramidal cell migration to their target field. *Left panel*, immunostaining for BrdU on hippocampal organotypic slices cultured for 1 day in vitro (DIV) without any treatment (control experiment; *left*), in the presence of NMDA antagonists (middle), and in the presence of $GABA_A$ antagonists (*right*). In the absence of any treatment, most BrdU+ neurons after 1 DIV have migrated to settle into the stratum pyramidale (SP). After 1 DIV, in the presence of MK801 or bicuculline, BrdU+ neurons that have failed to migrate are mainly distributed into the migration area (i.e., neuroepithelium [NE]/stratum oriens [SO]). Scale bar, 20 µm. *Right panel*, histogram illustrating the migration index obtained after treatment for 1 DIV with NMDA antagonists or $GABA_A$ antagonists compared with the untreated control experiment. The migration indexes are expressed (± SEM) as the ratio between the percentage of cells that reached the stratum pyramidale after 1 DIV and the percentage of cells that were still in the migration area (i.e., from the neuroepithelium to the stratum oriens), with the average of the control values being set to 10. SLM, stratum lacunosum moleculare; SR, stratum radiatum. $^{**}P < 0.001$. Modified from Manent and others (2005).

processes and losing their attachment to glial fibers. After a long stationary period within this layer, they extend their processes and reinitiate migration to reach their final destination in the internal granular layer (IGL).

Komuro and Rakic (1992) demonstrated that calcium influxes through N-type voltage-gated calcium channels play a crucial role in modulating the rate of granule cell movement in the ML, with these calcium transients being tightly correlated with granule cell movement. Because granule cells express receptors to the transmitters and activation of these receptors can alter calcium influxes, these authors have further investigated the role of receptor activation on migrating granule cells. They have demonstrated that spontaneous activation of NMDA receptors modulates the rate of granule cell migration, with the blockade with NMDA antagonists (D-AP5 and MK801) reducing the rate of movement and the frequency of calcium transients (Komuro and Rakic 1993; see Fig. 1). The blockade of other subtypes of ionotropic glutamate receptors (i.e., AMPA and kainate receptors) or $GABA_A$ receptors fails to modify the rate of migration (Komuro and Rakic 1993).

Kumada and Komuro (2004) further analyzed changes in the frequencies of calcium transients along the migratory pathway and observed that each phase of granule cell migration is characterized by a unique pattern of calcium transients. Any perturbation of these patterns is also likely to cause deficits in migration and in the acquisition of the appropriate layering.

Tangential Migration

Interneurons are generated in the germinal zones of the basal ganglia primordium (i.e., the medial, lateral, and caudal ganglionic eminences) and navigate tangentially into the developing cerebral cortex and hippocampus, covering long distances (for a review, see Kriegstein and Noctor 2004). The interneuronal migratory pathways within the neocortex have been investigated using multiple techniques, but the most precise descriptions of these pathways have emerged from the production of GAD67-EGFP KI mice (Tamamaki and others 2003). The analysis of these mice, expressing GFP under the control of the GAD67 promoter, has revealed that migrating interneurons navigate along 2 main cortical streams: 1) a deep route, located within the SVZ and lower IZ, and 2) a more superficial route, within the MZ and cortical SP (Tamamaki and others 2003; Tanaka and others 2003). Interneurons can also migrate radially (Nadarajah and others 2002) or obliquely (Tanaka and others 2003) between the main routes within the neocortex. In contrast to the neocortex, interneurons populate the hippocampus mainly via a superficial pathway below the MZ (Manent and others 2006).

Migratory cortical interneurons express functional $GABA_A$ (Metin and others 2000; Soria and Valdeolmillos 2002), $GABA_B$ (Lopez-Bendito and others 2003), and AMPA receptors (Metin and others 2000; Poluch and others 2001; Soria and Valdeolmillos 2002) but not NMDA

receptors (Metin and others 2000; but see Soria and Valdeolmillos 2002). The blockade of $GABA_B$ receptors results in an accumulation of tangentially migrating neurons in the VZ/SVZ of cortical explants (Lopez-Bendito and others 2003), and the activation of AMPA receptors affects the length of their leading processes (Poluch and others 2001). The modulation of interneuronal migration by transmitters has been investigated recently on cortico-hippocampal explants from GAD67-EGFP KI animals. In this preparation, incubation with AMPA receptor antagonists (NBQX, CNQX) impairs interneuronal migration to the hippocampus, reducing the number of cells able to migrate to this structure, whereas NMDA or $GABA_A$ receptor antagonists have no effects (Manent and others 2006; see Fig. 1). Interestingly, Metin and colleagues (2000) have shown that AMPA receptors expressed by interneurons migrating in the neocortical IZ are highly permeable to calcium because they apparently fail to express the GluR2 subunit. Similarly to granule cells migrating in the cerebellum (see above), calcium entry via those receptors might modify intracellular calcium levels in migrating interneurons, thus affecting the rate of movement of these neurons.

Rostral Migration

The SVZ lining the anterior border of the lateral ventricle is a germinal zone responsible for the genesis of the olfactory bulb neurons. In a process beginning during embryogenesis and continuing postnatally and in adulthood, this germinal zone gives rise to young neurons that migrate tangentially along the rostral migratory stream (RMS) up to the olfactory bulb (Alvarez-Buylla and Lim 2004). This peculiar mode of migration is also referred to as chain migration because neurons migrate within the RMS as chains of neurons, ensheathed by glial processes (Lois and others 1996; Wichterle and others 1997). When reaching the olfactory bulb, neurons detach from chains and start to migrate radially to their final destination layer within the bulb.

Labeling of newly generated neurons using retroviruses carrying GFP and patch-clamp recordings has been used to analyze rostral migration (Carleton and others 2003). Young neurons migrating tangentially within the RMS express functional $GABA_A$ and AMPA receptors and, when migrating radially within the olfactory bulb, start expressing NMDA receptors (Wang and others 2003; Carleton and others 2003). On time-lapse imaged acute slices, activation of $GABA_A$ receptors reduces the speed of tangential migration within the RMS, with the ambient GABA levels being essentially controlled by encapsulating glial cells (Bolteus and Bordey 2004; see Fig. 1).

Neurotransmitters and Calcium Dynamics

On a cellular level, neuronal migration is well established, as the migration of other cell types is based on a complex and coordinated reorganization of the cytoskeleton (microtubules and actin microfilaments) and a continuous sequence of adhesion and detachments. Intracellular Ca^{2+} concentration is an important coordinator of these intracellular processes (Doherty and others 2000; Gordon-Weeks 2004) so that $[Ca^{2+}]_i$ must be tightly controlled in migrating neurons. One of the best ways to control $[Ca^{2+}]_i$ in the maturing brain is provided by neurotransmitters via the activation of specific receptors. Thus, as commented before, in migrating cerebellar granule cells and cortical pyramidal neurons, the NMDA receptor plays an important role in increasing $[Ca^{2+}]_i$ (Kumada and Komuro 2004). The activation of calcium-permeable AMPA receptors in tangentially migrating interneurons should also result in $[Ca^{2+}]_i$ rises (Metin and others 2000; Soria and Valdeolmillos 2002). In addition, $GABA_A$ receptor activations should also increase $[Ca^{2+}]_i$ in migrating pyramidal cells, as this receptor has been shown to have a depolarizing action in immature neurons and to induce intracellular calcium rises due to the activation of voltage-gated calcium channels and NMDA receptors (Ben-Ari and others 1997).

The best link between intracellular calcium dynamics and neuronal migration has been provided by Komuro and Rakic (1996), when analyzing the migration of cerebellar granule cells. Using calcium imaging techniques, these authors demonstrated that migrating neurons displayed spontaneous transient calcium increases, whose frequencies and amplitudes positively correlated with the rate of granule cell migration. In this study, the block of calcium channels resulted in a reduction of intracellular calcium rises and a subsequent retardation of cell migration. Therefore, it is likely that neurotransmitter-mediated modulation of neuronal migration is related to a modulation of calcium transients, at least in this cell type. It is clear, however, that calcium actions would depend on a number of factors that include, among others, the following: the type of calcium activity generated (frequency, amplitude), the precise time at which it intervenes (cells are actively migrating or at rest), the location of the migrating cell at the time of exposure (leaving the germinative area, going through the migrating path, penetrating the final target), and the subcellular area concerned (the growing tip, the cytosol). Analysis of other cell types (i.e., dissociated cortical interneurons; Moya and Valdeolmillos 2004) failed to demonstrate a link between cell nucleokinesis and calcium rises induced by bath application of an agonist of kainate receptors. However, these results are inconclusive as a number of concerns require elucidation, particularly the type of spontaneous calcium transients observed in these migrating neurons and the mechanisms responsible for them. Only then can an evaluation of the repercussions of their induction or their block by specific pharmacological agents indicate whether calcium is a major player in their migration. The only thing that can be concluded today is that calcium transients effectively contribute to the migration of cerebellar granule cells and that more should be done to clarify whether calcium signaling is involved in the migration of other neuronal cell types.

Table 1. GABA and Glutamate Receptor-Mediated Modulations of Neuronal Migration

	Cerebellum	Neocortex/Hippocampus		RMS
	Granule Cells	Pyramidal Cells	Interneurons	Interneurons
$GABA_A$	No effect	+ and stop	No effect	—
NMDA	+	+	No effect	No effect
AMPA/kainate	No effect	No effect	+	No effect

Motility-promoting (+), inhibitory (–), or stop signals mediated by GABA and glutamate receptor activation are summarized as a function of the brain structures and neuronal subtypes considered. RMS, rostral migratory stream; NMDA, *N*-methyl-D-aspartate.

Transmitters as Developmental Signals: Diverse Modulations and Diverse Modes of Migration

Modulatory actions of transmitters during neuronal migration have been investigated on different neuronal subtypes using different experimental models. These studies have revealed predominant modulatory actions of GABA and glutamate, acting mainly through $GABA_A$ and NMDA receptors. As described in the previous sections, distinct transmitters acting on specific receptors exert different actions as a function of the neuronal subtype and mode of migration considered (see Table 1). According to these results, we can propose that the specific expression pattern of receptors is a typical feature of a given neuronal subtype migrating in a given migratory modality. Therefore, migrating neurons would express the adequate receptor pattern necessary to navigate and reach their appropriate destinations. Neurons migrating to the olfactory bulb represent an interesting illustration of this concept. Carleton and colleagues (2003) have investigated the migration of these neurons along the rostral migratory stream and demonstrated that these cells express distinct receptor patterns as a function of their migratory modality. Neurons tangentially migrating as neuronal chains within the RMS express functional $GABA_A$ and AMPA receptors, whereas neurons detaching from the chains to start migrating radially to their final destination express NMDA receptors. With their tangential migration being modulated by GABA acting through $GABA_A$ receptors (Bolteus and Bordey 2004), it is reasonable to hypothesize that this migration would also be modulated via AMPA receptor activation, as already shown for tangentially migrating interneurons in the hippocampus (Manent and others 2006). Furthermore, the radial part of the migratory pathway is likely to be modulated via NMDA receptor activation, but this remains to be investigated. It would also be interesting to address the same issue in the cerebellum, in which granule cells start first to migrate tangentially within the EGL, before starting their radial, glial-guided migration within the ML, with this latter stage being modulated by NMDA receptors (see above).

Finally, migrating neurons are not strictly restricted to a single migratory modality. If interneurons migrate mainly tangentially to their target fields and principal neurons migrate mainly radially, they can also adopt different migratory modalities along their journey. Principal neurons migrating within the neocortex provide the best illustration of this observation. These neurons start migrating radially with a bipolar morphology to exit to germinal zones and then transiently become multipolar within the SVZ/IZ before attaching to radial glial fibers to climb to their final destination within the cortical plate. During the multipolar stage, these neurons migrate independently of the glial fibers with extremely high dynamics (Tabata and Nakajima 2003), and the direction of their movements can be radial, tangential, and transversal. Modulatory actions of transmitters during the multipolar stage have not been investigated so far but are very likely to occur, with the intermediate zone being a zone where different subtypes of migrating neurons largely coexist. Tangentially migrating interneurons can also diverge from their main migratory pathways, being able to migrate radially to reach their final destination layers (undergoing pial-oriented migration or ventricle-oriented migration; Nadarajah and others 2002) or obliquely between the main routes (Tanaka and others 2003). The terminal migration of interneurons may also be modulated by transmitters, as this process requires an appropriate distribution within the cortical layers, maintaining the balance between excitation and inhibition. This will be discussed in the following sections.

Transmitters as Paracrine Messengers?

Numerous studies have investigated the role of neurotransmitters as developmental signals, highlighting their crucial roles during virtually all stages of brain construction (see Nguyen and others 2001). These studies have identified various actions played by transmitters, modulating proliferation, neuronal migration, synaptogenesis, and cell survival, but their modes of action, as well as their mode of release, are presently unknown. Prior to synapse formation and when the density of synapses is relatively low, neurotransmitters are obviously involved in a nonsynaptic mode of interneuronal communication. Demarque and colleagues (2002) have demonstrated that a nonconventional release of transmitters is involved in a nonsynaptic communication at perinatal stages. Synaptically silent immature hippocampal pyramidal neurons exhibit a tonic form of GABAergic activation, and the evoked release of GABA and glutamate generates a slow current

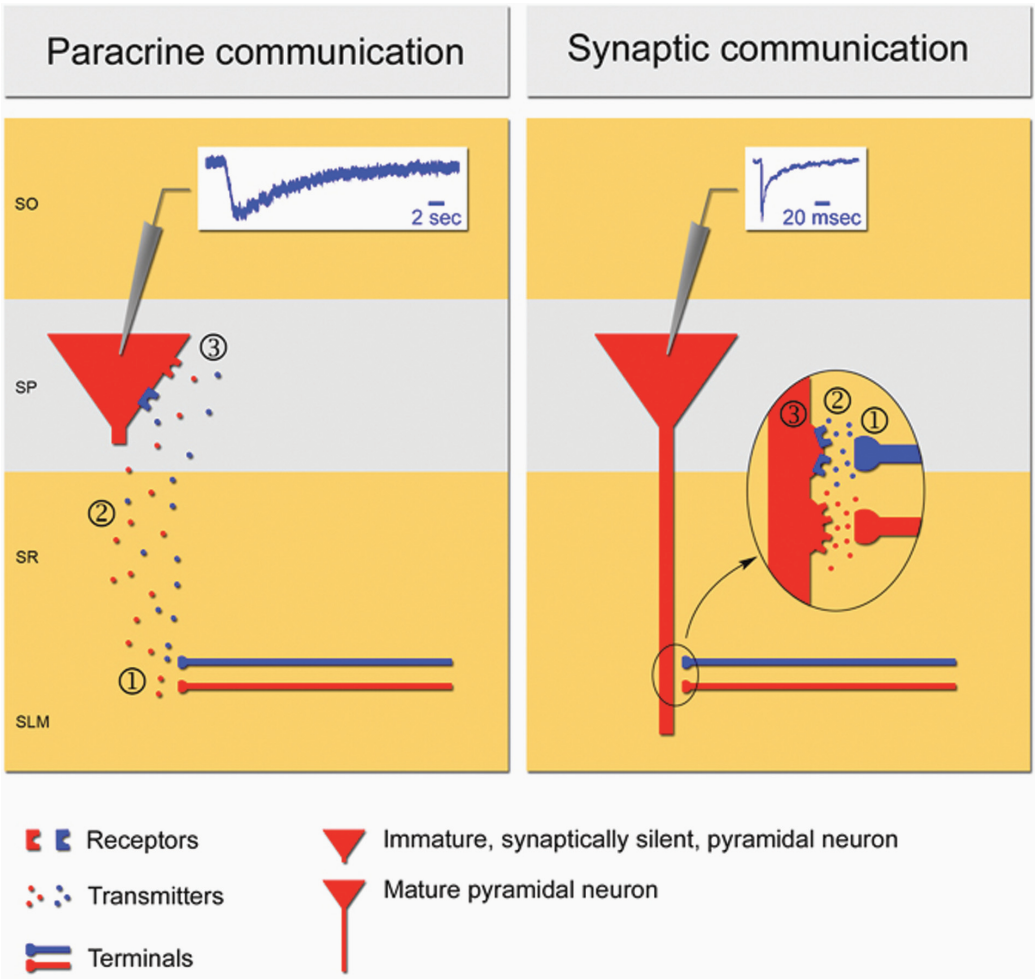

Fig. 3. Paracrine, nonsynaptic communication versus classical synaptic communication through neurotransmitters. *Left panel:* Transmitters, released in a nonconventional, soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)–independent manner *(1)*, diffuse over long distances *(2)* to activate receptors located on immature pyramidal neurons *(3)*, which are synaptically silent at that stage. Receptor activation generates large currents (as exemplified in the blue trace) with slow kinetics, lasting over seconds. Diffusion of transmitters is facilitated by the immaturity of the clearance mechanisms (neurotransmitter transporters). Ambient transmitters are thus able to tonically activate immature neurons that have no synapses. These tonic currents can be unmasked upon applications of transmitter receptor antagonists (not illustrated). *Right panel:* Transmitters, secreted in a conventional, SNARE-dependent manner *(1)*, diffuse into the synaptic cleft *(2)* to activate synaptic (and extra-synaptic) receptors located on pyramidal neuron apical dendrites *(3)*. Receptor activation generates conventional postsynaptic currents, as exemplified in the blue trace. These currents differ from the previous ones because of their several orders-of-magnitude shorter kinetics (in the range of milliseconds). Diffusion of transmitters out of the synaptic cleft is limited by neurotransmitter transporter actions. SO, stratum oriens; SP, stratum pyramidale; SR, stratum radiatum; SLM, stratum lacunosum moleculare.

primarily mediated by the activation of $GABA_A$ and, to a lesser degree, NMDA receptors. These transmitters are released independently of the calcium- and SNARE-dependent mode of transmitter secretion, as both the tonic and the slow current persisted after treatment with Ca^{2+} channel blockers, and are still observed in Munc18-1-deficient mice in which vesicular release is abolished (Verhage and others 2000). Recently, Manent and colleagues (2005) have demonstrated that the same non-canonical release of transmitters participates in the modulation of hippocampal pyramidal neuron migration. In organotypic hippocampal slice cultures, application of $GABA_A$ and NMDA receptor antagonists led to a strong impairment of neuronal migration, including in slices prepared from Munc18-1-deficient mice, suggesting a non-conventional origin of the transmitters involved.

Therefore, neurotransmitters act as paracrine messengers at embryonic stages (see Fig. 3): 1) they are released via nonconventional mechanisms, independently of the SNARE-dependent, vesicular mode of secretion of transmitters; 2) they diffuse within the extracellular space of the immature brain, with their diffusion being facilitated by the immaturity of neurotransmitter clearance systems (Demarque and others 2002, 2004); and 3) they act on

receptors displaying specific subunit compositions, thus conferring particular properties—that is, a greater affinity to transmitters and a lesser sensitivity to desensitization (see Owens and others 1999; Demarque and others 2002).

Transmitters displaying these particular properties have been demonstrated to play a role in the modulation of hippocampal pyramidal neuron migration (see above), and it is reasonable to propose that virtually all transmitter actions before synaptogenesis share these properties. The presence of a developmental sequence, involving first an immature, paracrine communication through transmitters and then the appearance of a mature, synaptic communication through transmitters, can also be hypothesized. The rationale for the existence of such a sequence would be the requirement of a long-distance communication contributing to an appropriate construction of neuronal networks (i.e., appropriate positioning and balance of excitatory and inhibitory neurons; see below), before the synaptic mode of communication appears. This also implies the existence of a developmental period where both modes of communication coexist and probably cooperate.

A Cross-Modulation of Interneuron and Pyramidal Neuron Migrations May Orchestrate Neuronal Networks Construction

In adult networks, balance between excitation and inhibition is essential to generate behaviorally relevant patterns and to prevent the occurrence of epileptic seizures. Recent data obtained in our group strongly suggest that the coordination between excitatory and inhibitory neurons most likely starts at a very early stage in the hippocampus. To reach their final destination within the developing brain, excitatory and inhibitory neurons have to migrate over long distances away from their germinal zones. With their periods of migration being largely coexistent and their migratory routes remarkably intermingled, it is reasonable to suggest that they already interact when migrating. These neurons express functional GABA and glutamate receptors, and the activation of these receptors modulates their migrations: 1) hippocampal pyramidal neuron migration is modulated through the activation of $GABA_A$ and NMDA receptors (Manent and others 2005), and 2) hippocampal interneuron migration is modulated through AMPA receptor activation (Manent and others 2006). With pyramidal neurons being an obvious source of glutamate and interneurons an obvious source of GABA, we could suggest that these two cell types cooperate to modulate their migrations. Glutamate released from pioneer glutamatergic neurons would thus facilitate the migration of GABAergic interneurons, which in turn would release GABA, facilitating the migration of glutamatergic neurons (see Fig. 4). This mode of communication through transmitters could represent a homeostatic mechanism, allowing the construction of an equilibrated hippocampal network in terms of number of each neuronal subtype and, consequently, in terms of excitation and inhibition.

We can also propose that this mechanism would also be involved in the acquisition of the appropriate cortical layering. As mentioned previously, migrating neurons could diverge from their major migratory roads, mainly to undergo their terminal migration to their target layers. Such migratory behaviors, diverging from the main routes, may be necessary for the acquisition of positioning information required to settle into the appropriate cortical layer. An interaction between migrating neurons relying on a paracrine mode of communication through transmitters could represent a good candidate. It is interesting to notice that cortical heterotopias generated in animals models using methylazoxymethanol (Chevassus-au-Louis and others 1998) or RNA interference knockdown of doublecortin (Ramos and others 2006) contain not only excitatory but also interneurons. Thus, heterotopias, constituted originally of pyramidal cells that failed to migrate radially to the cortical plate, also attract and retain migrating interneurons. Although speculative, it is tempting to suggest that the reciprocal interactions between glutamatergic and GABAergic systems are contributing with other factors to this cell population-dependent defect.

Neuronal Migration Defects and Neurotransmitter Receptors

According to the data discussed here, a perturbation of neurotransmitter and neurotransmitter receptor actions results in the genesis of cell migration defects (neurons remain close to the ventricle or stacked in intermediate locations). These neurons adopt ectopic positions, which are strongly reminiscent of cell migration defects observed in human patients (Barkovich and others 2005). It is thus plausible that some sporadic cell migration disorders result from alteration of neurotransmitters and/or neurotransmitter receptor dysfunction.

Neuronal migration disorders—characterized mainly by abnormal positioning of postmitotic neurons, remaining in the periventricular area, close to their place of genesis (nodular heterotopias), or adopting an intermediate final position, associated with an abnormal cortical layering (doublecortex, lissencephaly)—represent a major cause of developmental disabilities and severe epilepsy. The progress of high-resolution MRI techniques allows a better diagnosis of this condition in vivo, and it is thus estimated that up to 40% of children with drug-resistant epilepsy have cortical malformations (Guerrini 2006). The implication of cell migration defaults on dyslexia and autism has also been considered (Eckert 2004; Persico and Bourgeron 2006).

Some gene mutations implicating diverse types of proteins, including transcription factors and cytoskeletal proteins (Barkovich and others 2005), might lead to this type of migration deficits, and genetic counseling is now possible in a considerable number of patients. Are neurotransmitters/receptors contributing to these genetically associated alterations? The issue remains an open question, particularly after the publication of data obtained from knockout (KO) mice lacking GABA or vesicular release of transmitters. In fact, gross histological analysis of mice deficient for GABA-synthesizing enzymes (GAD65 and GAD67) did not reveal any significant alteration in cortical layer organization (Asada and others 1996, 1997). Also, the mutation of SNARE and SNARE-related proteins, which associated strong reduction or

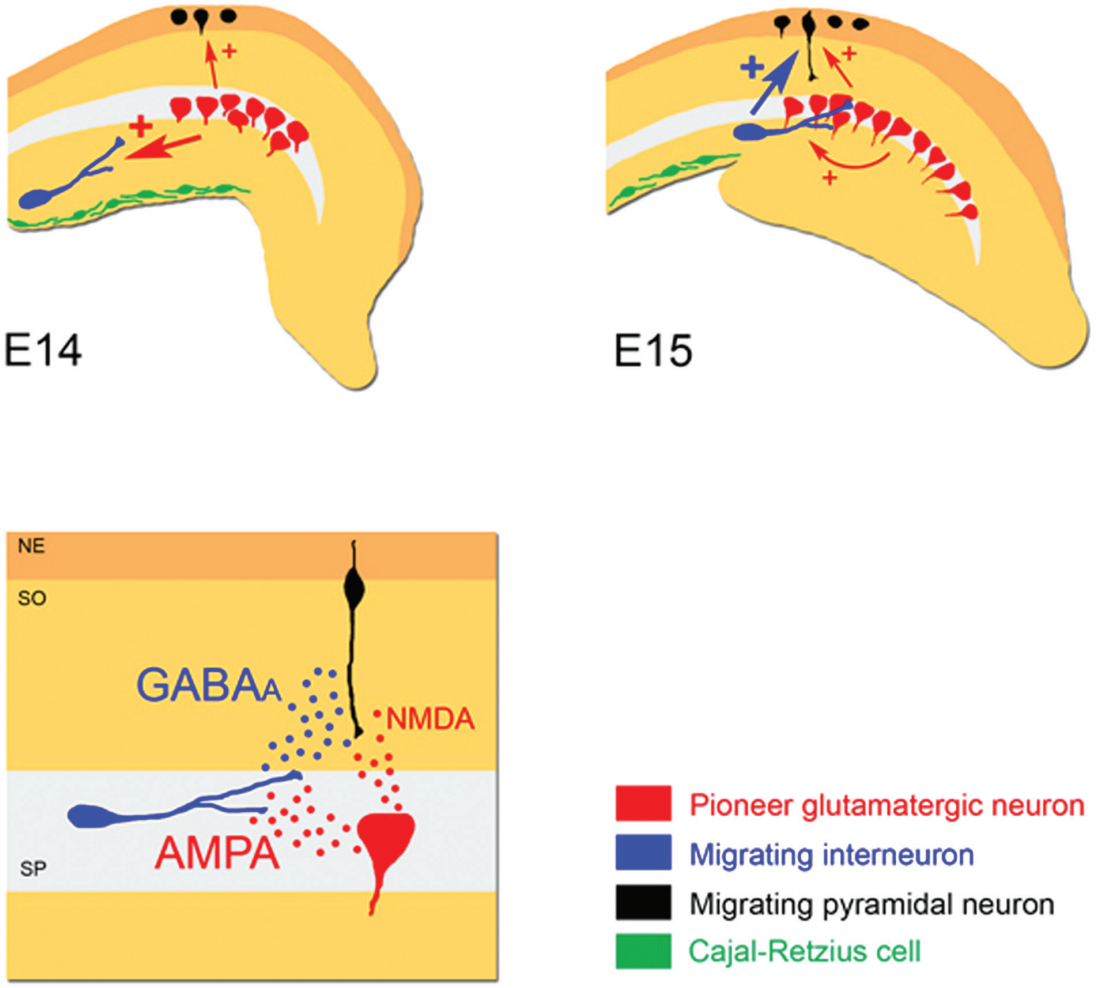

Fig. 4. A cross-modulation of interneuron and pyramidal neuron migrations may orchestrate neuronal network construction, a proposed model. Diagrams illustrate the reciprocal interactions between glutamatergic pyramidal neurons and GABAergic interneurons in the developing embryonic hippocampus. Pioneer pyramidal neurons (in red) are present in the hippocampal primordium before the arrival of interneurons (by E14). They likely release glutamate that exerts a positive influence on the migration of interneurons (in blue) via the activation of AMPA receptors. Cajal-Retzius cells (in green), located along the migratory pathway to the hippocampal primordium, would also release glutamate, influencing interneuronal migration. Once interneurons have entered the hippocampal plate (by E15), they likely release GABA, facilitating the migration of pyramidal neurons via the activation of $GABA_A$ receptors, with the cooperation of glutamate acting on NMDA receptors. More pyramidal neurons then reach the hippocampal plate, which in turn will help the migration of more interneurons. The bottom panel illustrates a positive cooperation between the two neuronal subtypes, cross-modulating their migrations to construct an equilibrated hippocampal network in terms of number of each neuronal subtype and, consequently, in terms of excitation and inhibition. SO, stratum oriens; SP, stratum pyramidale; NE, neuroepithelium.

complete abolition of neurotransmitter release through vesicular secretion, did not display any major alteration of cortical maturation during the embryonic life (Verhage and others 2000; Varoqueaux and others 2002). However, KO mice frequently experience compensatory mechanisms that may blur the conclusions, particularly when considering modulatory actions. In fact, glutamate might compensate for the lack of GABA on its action upon pyramidal cell migration, and it has been reported that immature brain cells release GABA and glutamate in a SNARE vesicular-independent manner (see below and Demarque and others 2002).

In addition to genetic mutations, environmental factors might have a strong impact on brain construction and may originate cortical developmental disorders. Much attention was dedicated to patients or animals exposed to irradiations (Roper and others 1997) or chemical antimitotic agents (Chevassus-au-Louis and Represa 1999). These factors likely perturb radial glial cells and, subsequently, the migration of principal neurons, thus originating periventricular neuronal ectopias (Roper and others 1997; Zhang and others 1995). Most interesting, the analysis of fetal alcohol syndromes induced in animals revealed the presence of cortical layer disorganizations and neuronal

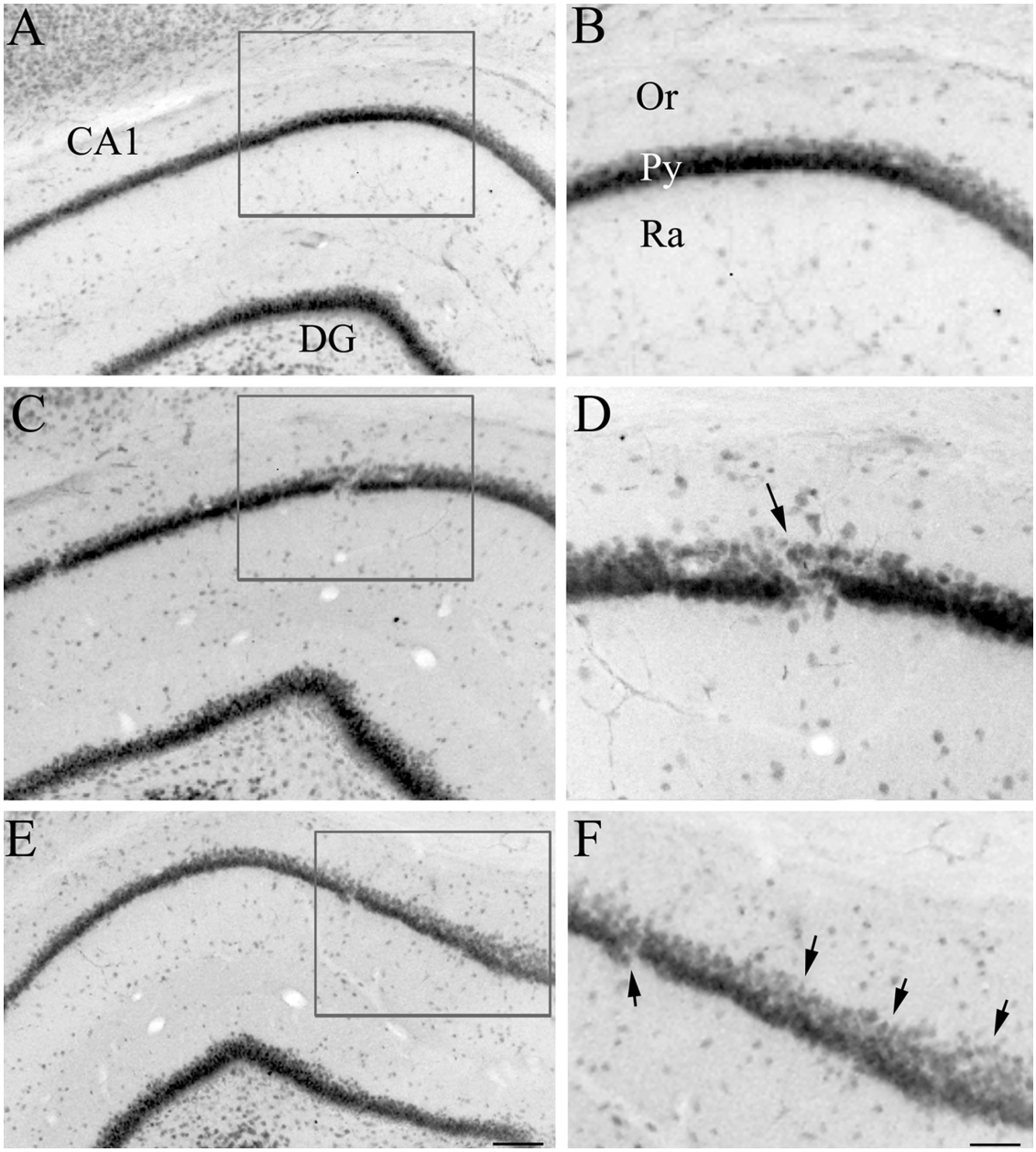

Fig. 5. Fetal exposure to antiepileptic drugs acting on GABA transmission causes cortical microdysplasias. NeuN immunostainings of a control hippocampal CA1 field (*A*, *B*), as observed in sections from a P30 rat born to a vehicle-treated mother, and two examples of hippocampal microdysplasias induced by prenatal exposure to two different antiepileptic drugs: (*C*, *D*) vigabatrin and (*E*, *F*) valproate. Interruptions in the CA1 lamination (arrow in *D* and right arrow in *F*) and clear neuronal dispersions were observed in offspring of pregnant rats treated with these GABA-acting drugs; many neurons failed to enter the pyramidal cell layer and distributed within the stratum oriens (arrows in *F*). Scale bar, 200 μm (*A*, *C*, *E*) and 100 μm (*B*, *D*, *F*). Modified from Manent and others (unpublished, 2007).

ectopias (Komatsu and others 2001; Sakata-Haga and others 2002), alterations that likely result from an action on $GABA_A$ (Wafford and others 1991; Harris and others 1995) and NMDA receptors (Lovinger and others 1989; Hoffman and others 1989). More recently, investigations performed in our laboratory revealed that pharmacological agents aimed to target the GABA system (some antiepileptic drugs) may perturb the migration of principal neurons in rats born to treated mothers (Manent and others unpublished, 2007). These data, in addition to stressing the regulatory role of transmitters in brain construction, raise concerns on the use of pharmacological drugs during pregnancy and underline the need for appropriate tests to evaluate possible teratogenic effects on brain maturation, an aspect that, with the exception of a few reports (Bittigau and others 2002; Manent and others (unpublished, 2007);

see Fig. 5), has received little attention. Interestingly, it has been reported that the offspring of mothers exposed to antiepileptic drugs display cognitive deficits and electroencephalogram abnormalities (Koch and others 1999; Viinikainen and others 2006). It is tempting to suggest that children exposed to this type of drugs during their fetal life would develop cell migration defaults that are associated with cognitive impairment. To our knowledge, there are no human data available to exemplify this issue, but different ongoing multicenter analyses are presently aimed to investigate the repercussions of prenatal exposure to antiepileptic drugs on cognitive functions. It would be interesting to propose, for children born to treated mothers and displaying cognitive impairment and developmental delay, careful magnetic resonance imaging analysis to evaluate the eventual presence of microdisgenesis.

Pursuing further the debate of genes and environment on brain maturation, it has been reported that environmental factors would result in phenotypic variability of single gene mutations (Wallace and others 1998). It is thus plausible that genetic and environmental factors jointly contribute to the expression of cortical developmental disorders, and depending on the action of transmitters, a migration breakdown would be enhanced or even reduced. Although very speculative, we may also propose environmental factors as capable for compensation of genetic-related migration defaults. For example, recent time-lapse analysis of the repercussions of DCX mutations on neuronal migration reported a function for DCX in the migration of newly generated neurons in the adult brain. Affected neurons migrating in the rostral migratory stream displayed, in fact, a reduced rate of movements so that they reached their final destination with a significant delay as compared to normal neurons (Koizumi and others 2006). As transmitters modulate the speed of migration, appropriated pharmacological agents would help to rescue the phenotype.

Conclusion

In conclusion, neurotransmitter actions and neurotransmitter receptor activation strongly modulate the migration of neurons from their place of birth to their final destination. Data discussed in this report strongly suggest that this modulation is aimed to control final positioning, timing, and numbers of neurons reaching their target fields. Neurotransmitters would also be involved in the genesis or expression of developmental alterations of cortical expression as cell migration disorders.

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