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REVIEW

GLUTAMATE AND GABA RECEPTOR SIGNALLING IN THE DEVELOPING BRAIN

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Abstract—Our understanding of the role played by neurotransmitter receptors in the developing brain has advanced in recent years. The major excitatory and inhibitory neurotransmitters in the brain, glutamate and GABA, activate both ionotropic (ligand-gated ion channels) and metabotropic (G protein-coupled) receptors, and are generally associated with neuronal communication in the mature brain. However, before the emergence of their role in neurotransmission in adulthood, they also act to influence earlier developmental events, some of which occur prior to synapse formation: such as proliferation, migration, differentiation or survival processes during neural development. To fulfill these actions in the constructing of the nervous system, different types of glutamate and GABA receptors need to be expressed both at the right time and at the right place. The identification by molecular cloning of 16 ionotropic glutamate receptor subunits, eight metabotropic glutamate receptor subtypes, 21 ionotropic and two metabotropic GABA receptor subunits, some of which exist in alternatively splice variants, has enriched our appreciation of how molecular diversity leads to functional diversity in the brain. It now appears that many different types of glutamate and GABA receptor subunits have prominent expression in the embryonic and/or postnatal brain, whereas others are mainly present in the adult brain. Although the significance of this differential expression of subunits is not fully understood, it appears that the change in subunit composition is essential for normal development in particular brain regions. This review focuses on emerging information relating to the expression and role of glutamatergic and GABAergic neurotransmitter receptors during prenatal and postnatal development.

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Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CNS, central nervous system; CP, cortical plate; CR, Cajal-Retzius; GABA, γ-aminobutyric acid; iGlu, ionotropic glutamate; IZ, intermediate zone; mGlu, metabotropic glutamate; NMDA, *N*-methyl-D-aspartate; RMS, rostral migratory stream; SVZ, subventricular zone; VZ, ventricular zone.

Key words: neurotransmitter receptors, AMPA, NMDA, kainate $GABA_B$ receptors, mGlu receptors, development.

Contents

The ability of our nervous system to learn, change and respond to the environment, reflects an underlying capability of neurons to dynamically alter the strengths of their connections. These connections, called synapses, are highly specialized sites of contact between presynaptic nerve terminals and postsynaptic neurons. Synapses contain a large variety of molecules at very high local densities, including neurotransmitter receptors, associated structural proteins and signaling molecules, whose precise organization gives rise to proper function. Among these synaptic molecules, neurotransmitter receptors will ultimately define the functionality of a synapse. Furthermore, many of the observed changes in synaptic transmission efficacy, that play a central role in processes such as learning and memory or neurodegeneration, are mediated by neurotransmitter receptors.

The present view of the central nervous system (CNS) has developed dramatically over the past few years and new principles regarding the role of neurotransmitter receptors in the developing CNS are beginning to emerge. The development of the CNS results from a well charac-

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terized temporo-spatial pattern of events that begins with neuronal proliferation, followed by migration, differentiation, and ending with synapse formation and circuit refinements. A growing body of evidence suggests that each step in that developmental sequence of the CNS involves both the appropriate expression and function of neurotransmitters and their receptors. Although glutamate and γ-aminobutyric acid (GABA) are the primary excitatory and inhibitory neurotransmitters in adulthood, it is now fairly well established that both are abundant and widespread early in embryonic life (Miranda-Contreras et al., 1998, 1999; Benítez-Diaz et al., 2003). Glutamate and GABA mediate their actions by the activation of ionotropic (ligand-gated ion channels) and metabotropic (G protein-coupled) receptors. Three subclasses of ionotropic glutamate (iGlu) receptors are known and are named after their selective agonists: i) α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), ii) *N*-methyl-D-aspartate (NMDA) and iii) kainate receptors (Hollmann and Heinemann, 1994). Sixteen functional subunits may assemble in tetrameric complexes to form the following receptors: GluR1–GluR4 for AMPA (that occur in two alternatively spliced versions, *flip* and *flop*); GluR5–GluR7 and KA1–KA2 for kainate; and NR1, NR2A–NR2D and NR3A–B for NMDA receptors (Hollmann and Heinemann, 1994). The metabotropic glutamate (mGlu) receptors consist of at least eight different subtypes ($mGlu_1$–$mGlu_8$), that have been classified into three groups based on their sequence homology, pharmacological profile and coupling to intracellular transduction pathways (Pin and Duvoisin, 1995; Conn and Pin, 1997). Group I mGlu receptors consist of $mGlu_1$, $mGlu_5$ and their splice variants ($mGlu_{1\alpha}$, β, c, d and $mGlu_{5a,b}$); group II receptors include $mGlu_2$ and $mGlu_3$; and group III consists of $mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$, and some splice variants.

Based on the presence of eight subunit families consisting of 21 subunits (α1-6, β1-4, γ1–4, δ, ϵ, π, θ, ρ1-3), the ionotropic GABA receptors ($GABA_A$ receptors) display an extraordinary structural heterogeneity. It is thought that most functional $GABA_A$ receptors *in vivo* are formed upon co-assembly of α-, β-, and γ-subunits (Macdonald and Olsen, 1994). The metabotropic GABA receptors ($GABA_B$ receptors) consist of two subunits: $GABA_{B1}$, which exists in alternatively spliced forms designated 1a, b, c, d and e, and $GABA_{B2}$ (reviewed by Billinton et al., 2001; Bowery et al., 2002). Physiological responses following activation of $GABA_B$ receptors require the co-assembly of $GABA_{B1}$ and $GABA_{B2}$ (reviewed by Couve et al., 2000; Bowery et al., 2002).

In this review, we summarize the current knowledge on the involvement of neurotransmitter receptors in neuronal signaling during development. We will focus on glutamate and GABA receptors, which are inextricably linked in the control of neuronal excitability, and discuss issues concerning their expression and role in the developing brain. Firstly, we will provide an overview of the diversity of glutamate and GABA receptor subunits and their developmental expression pattern, and then discuss their potential functions in the brain from proliferation to synapse formation.

Developmental expression of neurotransmitter receptor subunits

One indicator of the functional importance of neurotransmitter receptor subunit diversity comes from examining the subunit mRNA or protein changes seen during development. Although the exact changes in subunit expression vary with brain region, it now appears that many different types of neurotransmitter receptors are present in the embryonic brain, while others are dominant in the postnatal brain or in the adult brain.

AMPA receptor subunits. The GluR1 subunit is detected in the whole brain at embryonic day E15, and levels increase progressively during late embryonic and early postnatal days (Martin et al., 1998). Regionally, GluR1 increases in the cerebral cortex but decreases in the striatum with postnatal development. In the cerebellum, GluR1 is expressed transiently at particular time points postnatally, by both granule and Purkinje cells, but from P21 onwards these neurons have very low GluR1 levels (Martin et al., 1998; Fig. 1). The GluR2/3 subunits are also expressed in embryonic development, whereas the GluR4 subunit is mainly expressed in the late postnatal development and adult (Hall and Bahr, 1994; Furuta and Martin, 1999; Metin et al., 2000; Fig. 1). Concerning the isoforms of AMPA receptors, *flip* variants expression dominates before birth and continues to be expressed into adulthood, whereas *flop* variants are in low abundance before P8 and are up-regulated to about the same level as the *flip* forms in adulthood (Hollmann and Heinemann, 1994; Fig. 1).

NMDA receptor subunits. The functional NR1 subunit is ubiquitously present in the brain throughout pre- and postnatal development (Fig. 1), while the modulatory subunits (NR2A-D) are differentially expressed (Watanabe et al., 1993; Takai et al., 2003). The NR2A subunit is expressed postnatally and widely in the brain while the NR2B subunit is detected throughout the entire embryonic brain, with a restricted expression to the forebrain at postnatal stages (Fig. 1). The NR2C subunit appears postnatally and is prominent in the cerebellum; the NR2D subunit is mainly present in the diencephalon and the brainstem at embryonic and neonatal stages (Watanabe et al., 1993; Takai et al., 2003). The NR3 subunit is abundant within the late prenatal and early postnatal brain development (Sun et al., 1998).

Kainate receptor subunits. The mRNA for all kainate receptor subunits, except the KA-1 subunit, can be detected in the embryonic brain by E12 (Bahn et al., 1994). All subunits undergo a peak in their expression in the late embryonic and early postnatal period (Fig. 1). At the regional level, the GluR5 subunit shows a peak of expression around the period of birth in the sensory cortex, in CA1 hippocampal interneurons (stratum oriens), the septum, and in the thalamus, while the GluR6 subunit shows a prenatal expression peak in the neocortical cingulate gyrus. The KA-1 subunit appears with the development of the hippocampus and remains largely confined to discrete

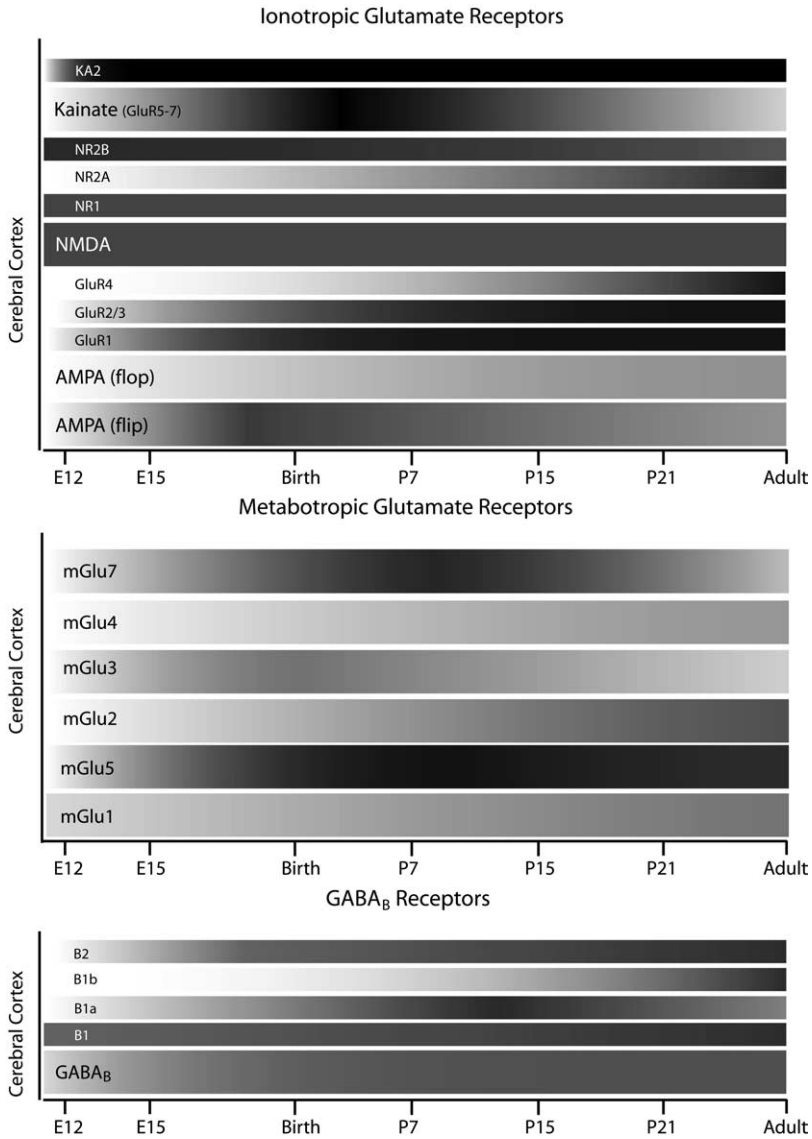

Fig. 1. Schematic representation of the expression of glutamate and GABA receptors throughout the developing rat cerebral cortex. The gradient in the gray scale shows the relative differences in the expression between the distinct subunits for each subclass of iGlu receptors, the distinct subtypes of mGlu receptors, and the distinct subunits of $GABA_B$ receptors, but not between the different receptor subclasses or subfamilies; for details see text. Differences in the onset of expression between substructures, e.g. cortical layers, have not been considered; for details see text. NMDA receptors are expressed relatively earlier than AMPA and kainate receptors. Regarding metabotropic receptors, $mGlu_1$ seems to be expressed relatively earlier than the other seven subtypes, whereas the $GABA_{B1}$ subunit of the $GABA_B$ receptors exceed that of the $GABA_{B2}$ subunit during embryonic development but equalizes in the adult brain. Embryonic and postnatal ages are expressed in days.

areas such as the CA3 region, the dentate gyrus, and subiculum, whereas the KA-2 subunit is found throughout the CNS from early embryonic stages (Fig. 1), remaining constant until adulthood (Bahn et al., 1994).

mGlu receptor subtypes. The expression of mGlu receptor subtypes is differentially regulated during development, showing distinct regional and temporal profiles. The two receptor subtype of group I, $mGlu_1$ and $mGlu_5$, are detected during embryonic development (Shigemoto et al., 1992; López-Bendito et al., 2002a; Fig. 1), albeit at low levels. However, while the level of $mGlu_1$ expression gradually increases during early postnatal days (Shigemoto et al., 1992; López-Bendito et al., 2002a), $mGlu_5$ expression increases perinatally, peaking around the second postnatal week and decreases thereafter to adult levels (Catania et al., 1994; Romano et al., 1996, 2002; Fig. 1). This different expression pattern is also detected at the level of their isoforms. Thus, it seems that $mGlu_{1\alpha}$ predominates during development, as $mGlu_{1\beta}$ and $mGlu_{1c}$ is mostly not detected until adulthood (Casabona et al., 1997). In contrast, the change in expression of $mGlu_5$ is associated with a decline in the $mGlu_{5a}$ splice variant and an increase in $mGlu_{5b}$, which dominates in adulthood (Minakami et al., 1995; Romano et al., 1996, 2002).

In addition, group II mGlu receptors are also differentially expressed. In the brain, $mGlu_2$ mRNA expression is low at birth and increases during postnatal development, whereas $mGlu_3$ is highly expressed at birth and decreases during maturation to adult levels of expression (Catania et al., 1994; Fig. 1).

Finally, with reference to group III mGlu receptors, the mRNA and protein expression for $mGlu_4$ is low at birth and increases during postnatal development (Catania et al., 1994; Elezgarai et al., 1999; Fig. 1). Similarly, $mGlu_{7a}$ levels are highest at P7 and P14, and then decline thereafter in cortical regions (Bradley et al., 1998).

$GABA_A$ receptor subunits. $GABA_A$ receptor subunit expression is differentially regulated during brain development, with each subunit exhibiting a unique regional and temporal developmental expression profile. Some of the 21 $GABA_A$ subunits dominate expression during embryonic development (e.g. α2, α3, and α5), whereas others dominate postnatally or in the adult brain (Laurie et al., 1992; Fritschy et al., 1994). For example, the expression of the α1 subunit is low at birth, but increases during the first postnatal week, whereas the α2 subunit decreases progressively (Fritschy et al., 1994). Additionally, the α5 subunit is found throughout pre- and postnatal development (Killisch et al., 1991). The β2/3 subunits are ubiquitously expressed during development, indicating their association with α subunits in distinct receptor subtypes (Fritschy et al., 1994). The γ1 and γ3 subunits expression levels drop markedly during development, whereas γ2 expression is widespread and remains mostly constant throughout development (Fritschy et al., 1994). Although the significance of the differential expression of $GABA_A$ receptor subunits is not completely understood, it seems that subunit switching in certain brain regions is essential for normal development (Culiat et al., 1994; Gunther et al., 1995).

$GABA_B$ receptor subunits. *In situ* hybridization and immunohistochemical studies have defined a pattern of early and strong $GABA_{B1}$ receptor expression in discrete brain regions during embryonic development (López-Bendito et al., 2002b, 2003, 2004b; Kim et al., 2003; Martin et al., 2004; Panzanelli et al., 2004). $GABA_{B1}$ receptor mRNA is intensely expressed by E11, and at E12 is detected in the hippocampal formation, cerebral cortex, intermediate and posterior neuroepithelium, and the pontine neuroepithelium (Kim et al., 2003; Martin et al., 2004). Furthermore, the most widely studied isoforms of the $GABA_{B1}$ subunit, $GABA_{B1a}$ and $GABA_{B1b}$, seem to be developmentally regulated, with $GABA_{B1b}$ being the most abundant isoform in the adult, while $GABA_{B1a}$ dominates during postnatal development (Fritschy et al., 1999; Fig. 1). However, $GABA_{B2}$ receptor mRNA and protein are not detected at the same time period, as the expression of the $GABA_{B1}$ subunit, whose isoforms greatly exceed that of the $GABA_{B2}$ subunit during embryonic development but equalizes in most regions in the adult brain (Kim et al., 2003; López-Bendito et al., 2002b, 2004b; Martin et al., 2004; Panzanelli et al., 2004; Fig. 1). Thus it is likely that the $GABA_{B1}$ subunit is more important than the $GABA_{B2}$ subunit in the early development of the CNS. Indeed, it appears that $GABA_B$ receptor subunits are not coordinately regulated during development. Despite the fact that functional $GABA_B$ receptor requires heterodimerization of $GABA_{B1}$ and $GABA_{B2}$ subunits, the expression of each of them is under independent control during embryonic development (Martin et al., 2004).

Neurotransmitter receptor signaling in cell proliferation

Proliferation of neuronal progenitors is one of the fundamental developmental processes responsible for generating the correct number of cells of each type in the correct sequence in the brain. Both cell-intrinsic and -extrinsic factors contribute to changes in cell production and affect cerebral cortical growth. Among other extracellular molecules, neurotransmitter receptors have been implicated in the extrinsic regulation of cell proliferation in the developing telencephalon (see review by Cameron et al., 1998; Nguyen et al., 2001; Owens and Kriegstein, 2002).

Functional iGlu receptors emerge during terminal cell division and early neuronal differentiation of rat neuroepithelial cells (Maric et al., 2000). Several studies have also shown that both NMDA and non-NMDA glutamate receptors are expressed in early postmitotic neurons (see review by Lauder, 1993; Bardoul et al., 1998), and that glutamate can inhibit DNA synthesis in cells proliferating at the cortical neuroepithelium when AMPA/kainate receptor are activated (LoTurco et al., 1995). However, proliferation of striatal neuronal progenitors is promoted by an NMDA receptor-dependent mechanism but not AMPA/kainate receptors at the ventral telencephalon (Luk et al., 2003).

AMPA responses are first observed in terminally dividing neuronal progenitors which begin to express Tuj1 (an antigen which is expressed by neuronal precursors) near the time of terminal division. Postmitotic neurons express both AMPA/kainate and NMDA receptors (Maric et al., 2000). Taken together these results suggest that the appearance of functional iGlu receptors may regulate the transition from proliferation to postmitotic neuronal differentiation.

The role of NMDA receptor activation controlling cell proliferation has also been shown to occur in brain regions that retain a neurogenic population of cells through life. This is the case in the dentate gyrus of the hippocampus, in rodents (Cameron et al., 1995), primates (Gould et al., 1998) and human (Eriksson et al., 1998). Several *in vivo* studies have shown that blockage of NMDA receptors during either the first postnatal week or in adult rats, increases cell proliferation in the hippocampus; affecting mainly granule cells (Gould et al., 1994; Cameron et al., 1995). However, the mechanisms by which glutamate decreases dentate gyrus cell proliferation remains unknown. In relation to the possible involvement of mGlu receptors, it has also been shown the presence of $mGlu_5$ receptor in zones of active neurogenesis both in the prenatal and postnatal brain (Di Giorgi Gerevini et al., 2004).

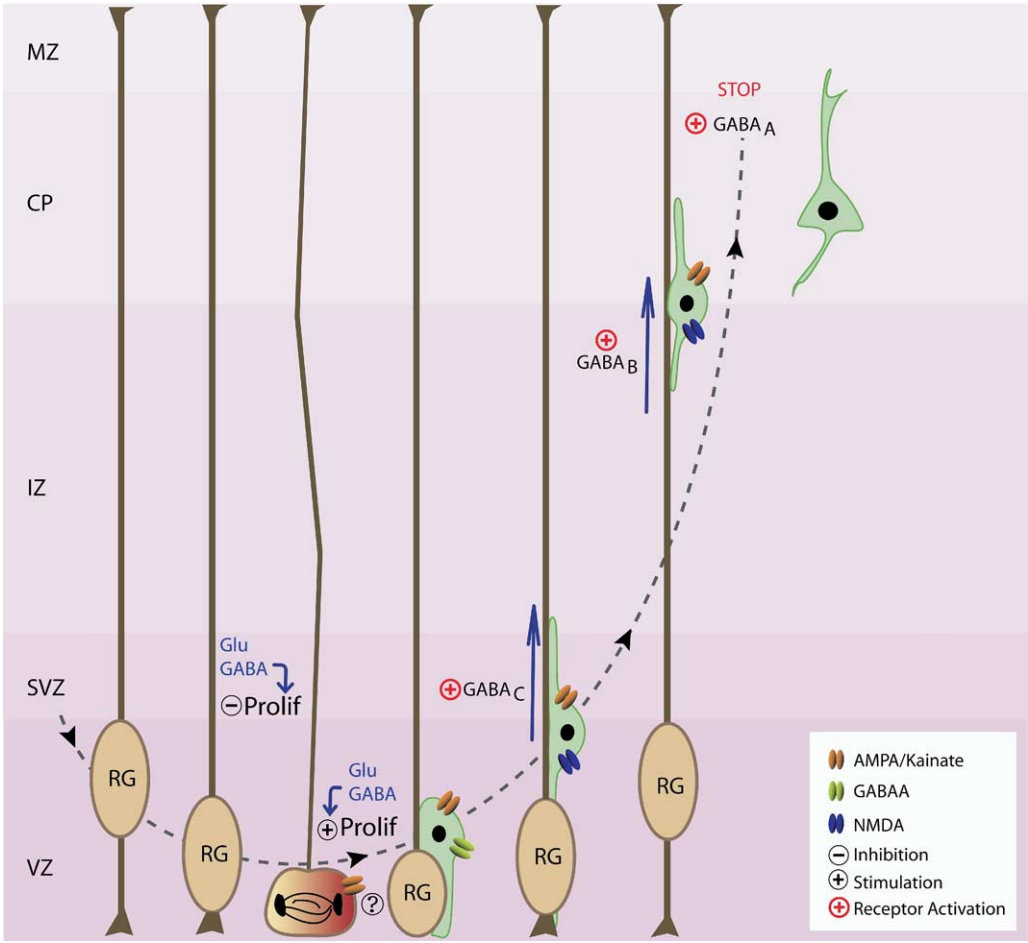

Fig. 2. Neurotransmitter receptors are involved in the Prolif and migration of cortical neurons. AMPA responses are first observed in terminally dividing neuronal progenitors while postmitotic neurons (green cells) express both AMPA/kainate and NMDA receptors. Activation of GABA and Glu receptors by GABA and Glu, respectively, has been shown to shorten the cell cycle of VZ progenitors (black circled positive symbol), while the Prolif in the SVZ is markedly decreased in response to GABA (black circled negative symbol). Neurotransmitter receptor activation has been reported to influence neuronal migration of cortical neurons at early stages of development. Thus, $GABA_C$ and $GABA_B$-like receptor activation (red circled positive symbol) stimulates migration of neurons from the VZ and IZ, respectively, whereas $GABA_A$ receptor activation arrests migration as neurons approach their target destinations in the CP. The U-shape discontinuous line with arrows represents the direction followed by the cells types during Prolif and migration. The gradient in the background color represents the different cortical layers. Glu, glutamate; MZ, marginal zone; Prolif, proliferation; RG, radial glia.

Regarding the GABAergic system, several types of $GABA_A$ receptor transcripts and subunits have been described as components of functional $GABA_A$ receptors in rat neuroepithelial cells, neuroblasts and glioblasts, during spinal and cortical neurogenesis (LoTurco et al., 1995; Ma and Barker, 1995; Ma et al., 1998; Serafini et al., 1998; Verkhratsky and Steinhauser, 2000). In precursor cells, in the neocortical proliferative zone, activation of $GABA_A$ receptors has been shown to influence DNA synthesis (LoTurco et al., 1995; Haydar et al., 2000). A more recent study has pointed to a more complicated scenario. Using organotypic mouse slice cultures in which the spatial separation between the ventricular zone (VZ) and subventricular zone (SVZ) of the cerebral cortex has been maintained, inherent differences between VZ and SVZ progenitors in their physiological responses to GABA or glutamate were observed (Haydar et al., 2000). Exogenously applied GABA and glutamate shortened the cell cycle of VZ progenitors; this effect suggesting a mediation by $GABA_A$ or AMPA/kainate receptors. Surprisingly, in contrast to these findings, proliferation in the SVZ markedly decreased in response to GABA, glutamate, and their agonists (Fig. 2). Thus, depending on the cortical compartment, GABA and glutamate have differential effects on cortical cell proliferation. Altogether, these results suggest that in cultured progenitor cells of the developing neocortex, GABA and glutamate regulate cell proliferation by providing a feedback signal that controls division (Fig. 2). Additionally, a GABA-dependent cell proliferation has also been demonstrated in the hippocampus (Ben-Yaakov and Golan, 2003).

The exact mode of GABA or glutamate action is still unresolved. Nevertheless, functional GABAergic-signaling components among differentiating neurons and their capacity to release GABA from both cell body and growth cone compartments emerge during neuronal lineage pro-

gression (Maric et al., 2001). Those postmitotic cells could be the source of GABA or glutamate that leads to the activation of GABA and glutamate receptors expressed by mitotic cells in the proliferative zones. Regardless of the subcellular compartment, it seems that at least GABA can be released in a paracrine manner to active its receptors (Demarque et al., 2002), as synapses are still not present. Other interesting questions as how are GABA and glutamate concentrations regulated or what kind of intracellular signaling mechanisms are involved in their activation are still unanswered.

Involvement of neurotransmitter receptor in neuronal migration

After division, most cortical neurons migrate from their site of origin to their final destination in the cerebral cortex. This neuronal movement is essential for the establishment of normal brain organization (see for instance Hatten, 1999). In the developing cerebral cortex, glutamatergic projecting neurons are primarily generated in the VZ and then move to the developing cortical plate (CP) by means of "radial migration" (see review by Marín and Rubenstein, 2001). Most GABAergic interneurons, however, originate mainly in the medial ganglionic eminence of the ventral telencephalon and follow tangential migratory routes through the intermediate zone (IZ) to reach the cortex (see review by Parnavelas, 2000; Marín and Rubenstein, 2001; Fig. 3). However, the caudal ganglionic eminence has been recently demonstrated to give rise to a distinct population of GABAergic interneurons (Nery et al., 2002; López-Bendito et al., 2004a).

Neurotransmitter receptor activation has been reported to influence neuronal migration of cortical neurons at early stages of development. The presence of some of these neurotransmitter receptors in the embryonic cerebral cortex has been shown by *in situ* hybridization and immunohistochemistry (Behar et al., 2001; López-Bendito et al., 2002b; Fig. 3). In the following sections, we will review the role of neurotransmitter receptors in the processes of neuronal migration in the forebrain.

Radial migration. Due to its early expression pattern, glutamate is a likely candidate to play a role as a chemoattractant signal in the developing mouse cerebral cortex. An assay measuring the effects of glutamate on the migration of acutely dissociated murine embryonic cortical cells, revealed stimulation of the migration of cortical neurons to a 10-fold greater extent than GABA (Behar et al., 1999). In the cerebellum, if NMDA receptors are blocked by specific antagonists or by high Mg^{2+} concentration, the granule cell migration from the external to the internal granule layer is retarded (Rossi and Slater, 1993). Conversely, an increase of NMDA or glycine concentration increases this process (Komuro and Rakic, 1993).

Some illuminating results on the role of neurotransmitter receptors on cortical radial migration, came from a series of pharmacological studies, which showed the influence of the activation of GABA receptors in neuronal motility and migration in both dissociated cells and organotypic slice cultures (Behar et al., 1996, 2000, 2001). In cultured rat brain slices, it has been determined that $GABA_C$ and $GABA_B$-like receptor activation stimulates migration of neurons from the VZ and IZ, respectively, whereas $GABA_A$ receptor activation arrests migration as neurons approach their target destinations in the CP (Behar et al., 1998). Altogether these data show that activation of neurotransmitter receptors, independent of the brain area or neuronal phenotype, plays a role in controlling the migration of neurons.

Tangential migration. The cellular and molecular mechanisms controlling tangential migration of cortical interneurons are still relatively unknown. It has been suggested that activation of AMPA receptors leads to neurite retraction in tangentially migrating interneurons (Poluch et al., 2001). In addition, tangentially migrating cells in the cerebral cortex posses functional NMDA, non-NMDA and $GABA_A$ receptors whose activation leads to changes in $[Ca^{2+}]_i$ (Soria and Valdeolmillos, 2002). However, the relationship between these changes in $[Ca^{2+}]_i$ signaling and the actual process of tangential migration is still unclear.

Several studies though have provided some illuminating ideas on the role of GABA receptors in tangential migration. Interestingly, one of these studies involved the activation of neurotransmitter receptors and the end result, in particular, reinforced the role of $GABA_B$ receptors in migration of neurons (López-Bendito et al., 2003). Using *in vitro* embryonic rat organotypic cultures, in combination with immunohistochemical techniques, it was shown that blockade of $GABA_B$ receptor modified the distribution of tangential migratory interneurons within the cortex (López-Bendito et al., 2003; Fig. 3). Additionally, other studies have shown the functionality of some of these neurotransmitter receptors, in the tangentially migratory interneurons (Metin et al., 2000; Soria and Valdeolmillos, 2002). For example, GABAergic calbindin-positive IZ cells seem to express inwardly rectifying calcium-permeable AMPA receptors, but not NMDA receptors (Metin et al., 2000; Fig. 3). Likewise, these cells displayed electrophysiological responses to $GABA_A$ agonists.

Another population of neurons that adopt a tangential mode of migration to reach their final target is the precursors of olfactory interneurons. These interneurons are born in the embryonic subpallium (Altman, 1969; Lois and Alvarez-Buylla, 1994) and their migration continues through adulthood, providing a constant supply of new GABAergic local circuit neurons to the olfactory bulb (Lois and Alvarez-Buylla, 1994). Migration of olfactory interneurons in the adult occurs along a highly restricted route termed the rostral migratory stream (RMS; Lois and Alvarez-Buylla, 1994; Kornack and Rakic, 2001). A recent study pointed out the possibility that GABA may also affect these neuronal progenitors via the activation of specific receptors (Wang et al., 2003). Every neuronal progenitor responded to GABA via picrotoxin-sensitive $GABA_A$ receptor activation, demonstrating that the neuronal progenitors of the SVZ/RMS contain and are depolarized by GABA.

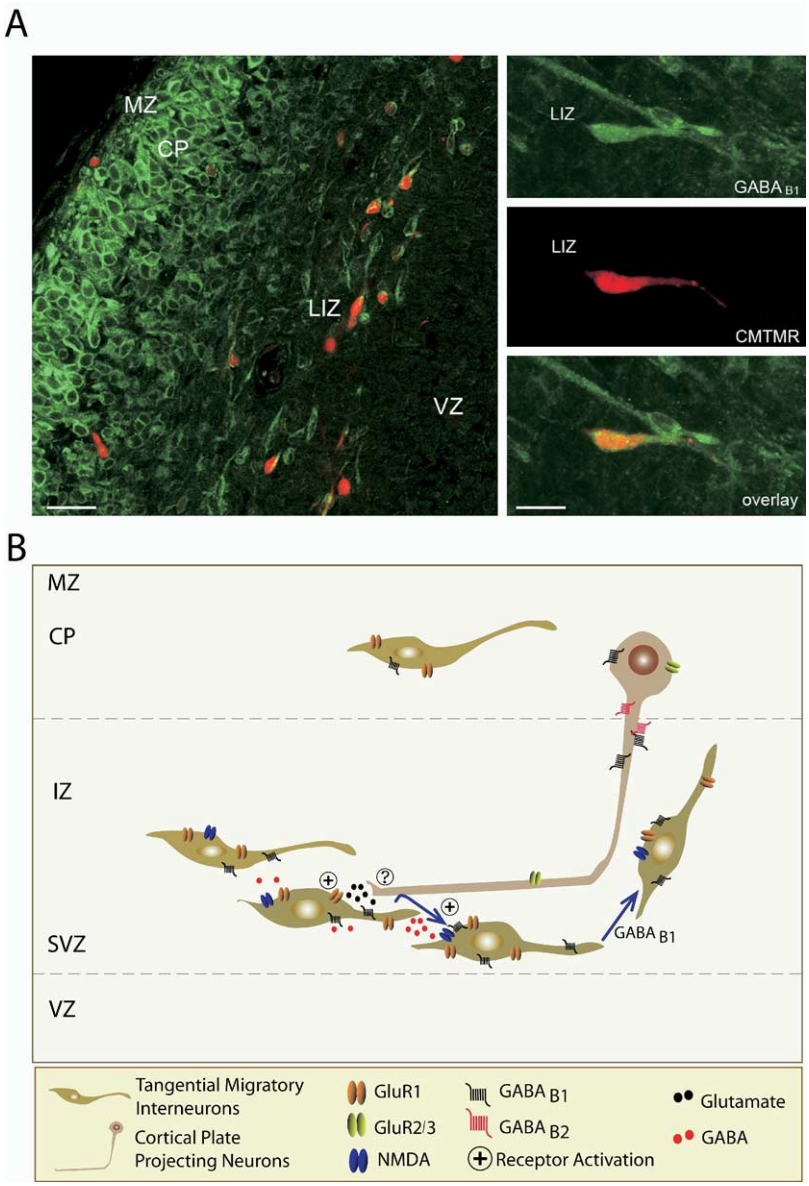

Fig. 3. Neurotransmitter receptors are involved in the tangential migration of cortical interneurons. Tangentially migrating interneurons express iGlu receptors in addition to GABA receptors (see legend in Fig. 3B). (A) Expression of $GABA_{B1}$ receptor subunit (green) in migratory interneurons coming from the ganglionic eminence, labeled in red with a cell-tracker (CMTMR). Note the high expression of this receptor subunit in the plasma membrane and cytoplasm of tangentially orientated cells in the LIZ (insets) and in cells in the CP and MZ. (B) Diagram showing the expression and distribution of iGlu receptors and $GABA_B$ receptors in CP cells and tangentially migrating interneurons. CP cells may release glutamate that could activate (black positive symbol) iGlu receptors expressed in the tangentially migrating interneurons. This activation may lead to GABA release from these cells and to the activation of its GABA receptors and those expressed in nearby cells. The blockade of $GABA_B$ receptor leads to an accumulation of interneurons at the proliferative zones of the cortex suggesting that the activation of this receptor is important for the transition of the interneurons from the LIZ to the CP of the cortex. MZ, marginal zone.

This thus directly suggests that this event may constitute the basis for a paracrine signal among neuronal progenitors to dynamically regulate their proliferation and/or migration.

Role of neurotransmitter receptors in early neuronal differentiation

In addition to proliferation and migration, several aspects of neuronal differentiation appears to be regulated by early glutamate- and GABA-mediated signaling. For instance, one of the most important cell types during early cortical neuronal differentiation are the Cajal-Retzius (CR) cells. Among the earliest generated population of neurons in the developing neocortex, CR cells have been implicated in regulating cortical lamination. In rodents, CR cells are transient, being present only up to 2–3 weeks after birth. They secrete reelin (Reln, an extracellular matrix molecule), whose absence in the mouse mutant *reeler* causes

a severe cortical laminar disruption (see review by Frotscher, 1998; Curran and D'Arcangelo, 1998; Tissir and Goffinet, 2003). The molecular cascade acting downstream of Reln is just beginning to be understood (Walsh and Goffinet, 2000). However, the functional mechanisms that regulate Reln synthesis and secretion have been little explored. CR cells express diverse types of neurotransmitter receptors, including iGlu receptors and $GABA_A$ receptors (Schwartz et al., 1998; Mienville and Pesold, 1999). Recently, the expression of the mGlu receptor 1α, $mGlu_{1\alpha}$, in CR cells (Martínez-Galán et al., 2001; López-Bendito et al., 2002a) and the existence of functional $mGlu_1$ in layer I cells of the postnatal mouse cerebral cortex was established (Martínez-Galán et al., 2001). Postnatal CR cells incur a dramatic increase in their NMDA receptor density, which ultimately may trigger their death. The fact that *in vivo* pharmacological blockade of NMDA receptors curtailed the disappearance of CR cells (Mienville and Pesold, 1999) strongly supports such a hypothesis.

Apart from the correct positioning and laminar acquisition of cortical neurons, glutamate causes a graded series of changes in pyramidal neuron cytoarchitecture inducing a selective inhibition in dendritic outgrowth and dendritic pruning at subtoxic levels. Some studies have also reported that NMDA receptor activation promotes neurite outgrowth from cerebellar granule cells (Pearce et al., 1987) and dendritic outgrowth and branching of hippocampal cells (Mattson et al., 1988; Brewer and Cotman, 1989; Wilson et al., 2000). Furthermore, $GABA_A$ receptor activation has also been shown to promote neurite outgrowth and maturation of GABAergic interneurons (Barbin et al., 1993; Marty et al., 1996). In addition it is seen to regulate the morphological development of cortical neurons through membrane depolarization and increases in $[Ca^{2+}]_i$ (Maric et al., 2001).

Neurotransmitter receptor signaling during synaptogenesis

The establishment of neural networks begins with growing axons recognizing their postsynaptic targets, thus forming synaptic contacts. This process can be divided into two separate phases: the first one (synapse formation) comprises the establishment of functional synaptic communication, and the second phase (synapse maturation) comprises the functional and morphological differentiation of synapses; both phases requiring tight communication between pre- and postsynaptic elements. How specific pre- and postsynaptic elements are differentiated, how synaptic contacts are generated developmentally and how these synapses are remodeled and maintained in mature brain seems to be in part mediated by the action of neurotransmitter receptors. A complete description on the involvement of NMDA and AMPA receptors in the formation, stabilization, maturation and elimination of synapses has been extensively reviewed elsewhere (see for instance Bolton et al., 2000; Lee and Sheng, 2000; Zhang and Poo, 2001; Cohen-Cory, 2002; Garner et al., 2002). Although the involvement of mGlu receptors in such processes is unknown, it has been recently suggested that they may also participate in synapse-stabilizing responses (Miskevich et al., 2002). Additionally, a description on the role of $GABA_A$ receptor subunits in synaptogenesis has also been extensively reviewed recently (see for instance Ben-Ari, 2002; Owens and Kriegstein, 2002; Fritschy et al., 2003; Meier, 2003). Altogether, those reviews outline that the assembly of CNS synapses likely involve a complex interplay of cell–cell adhesion, interneuronal signaling and site-specific recruitment of protein complexes. Furthermore, activity-dependent mechanisms control postsynaptic level of neurotransmitter receptors, with different mechanisms used for the synaptic targeting of distinct receptor types.

Much less is known, however, about the acquisition of different glutamate and GABA receptor subunits occurring during synapse formation, and how they accumulate and change at synapses to reach their final distribution pattern during synapse maturation and adulthood. In the next section, we will concentrate on such processes.

Acquisition and localization of neurotransmitter receptors at synapses

A critical aspect in the development of glutamatergic and GABAergic synapses is the progressive recruitment and subsequent accumulation of neurotransmitter receptors at their functional site. Such processes are important, because proper function of synaptic transmission at any given synapse, depends on adequate placement of neurotransmitter receptors of the appropriate number and type, in the neuronal membrane. The differential regulation of the distinct subunits during pre- and postnatal development (see Developmental expression of neurotransmitter receptor subunits) may favor the correct acquisition and accumulation processes of receptor complexes.

Glutamatergic synapses. Electrophysiological and immunohistochemical studies have shown that NMDA receptors are expressed firstly in glutamatergic synapses. Early in postnatal development, and during development, synapses acquire AMPA receptors with little change in NMDA receptor numbers (Golshani et al., 1998; Petralia et al., 1999). With regard to their localization, during postnatal development and adulthood, AMPA and NMDA receptors are concentrated at the postsynaptic specialization (Fig. 4). However, while AMPA receptors seem to be evenly distributed along the postsynaptic specialization (Nusser et al., 1998b; Somogyi et al., 1998), NMDA receptors are preferentially distributed to the center of it (Somogyi et al., 1998; Racca et al., 2000). Interestingly, NMDA receptors have been found on membranes postsynaptic to GABAergic terminals (Fig. 4) in the adult hippocampus (Gundersen et al., 2004), though no information is yet available about the factors controlling their recruitment in inhibitory synapses during development. Finally, the acquisition and arrangement of kainate receptors at synapses remains to be fully established. It is well known, however, that the KA-1 and KA-2 subunits are located at synaptic sites, as well as at presynaptic sites in the adulthood (Darstein et al., 2003; Fig. 4).

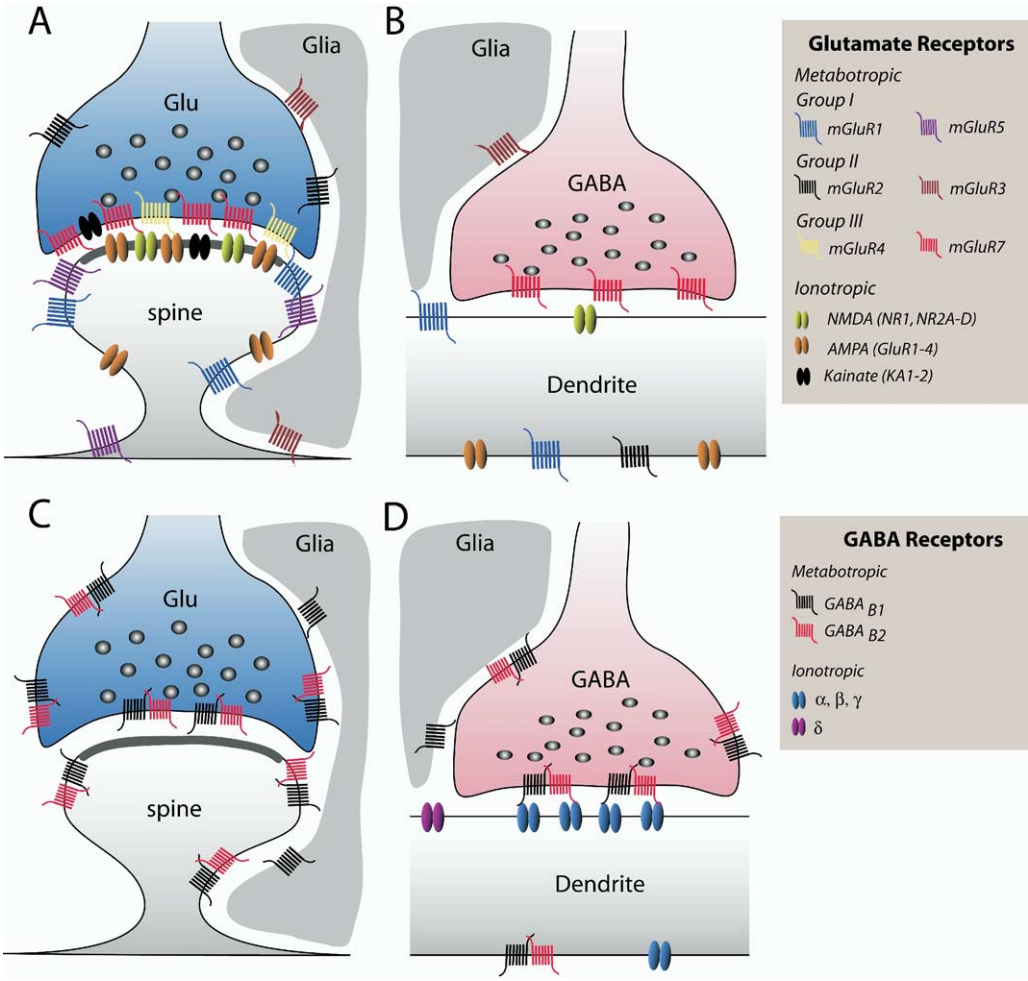

Fig. 4. Schematic diagrams showing the location of glutamate and GABA receptors at synapses in the cerebral cortex during postnatal development and adulthood. Panels A and B show the localization of glutamate receptors at excitatory and inhibitory synapses, respectively. Panels C and D show the localization of GABA receptors at excitatory and inhibitory synapses, respectively. The precise localization of the different glutamate and GABA receptor subunits varies among brain regions and cell types. Therefore, the schematic diagrams are not representative of all glutamatergic or GABAergic synapses. NMDA, AMPA and kainate receptors are concentrated in the postsynaptic specialization, as well as extrasynaptically (panel A). Early in postnatal development, and during development, synapses acquire AMPA receptors with little change in NMDA receptor numbers. However, group I mGlu receptors are absent from the postsynaptic specialization, occurring peri- or extrasynaptically (panel A). Group II mGlu receptors occur in the preterminal portion of axon terminal, whereas group III mGu receptors are found in the presynaptic active zone (panel A). During postnatal development, mGlu receptors progressively concentrate at those subcellular compartments to reach their final density in the adult brain. $GABA_A$ receptor subunits are concentrated at synapses opposite to GABA releasing terminals (panel D). In contrast, $GABA_B$ receptors can be present at pre- and postsynaptic sites (panels C and D). They are mainly found associated with glutamatergic synapses (panel C).

The acquisition and distribution of mGlu receptors during development seems to be different to that described for iGlu receptors. This may be because mGlu receptors are absent from the postsynaptic specialization. Electrophysiological studies (Golshani et al., 1998) have shown that functional mGlu receptors are detected in cortical synapses from birth (approximately at the same time as functional NMDA receptors), although only after the first postnatal week could slow EPSPs mediated by mGlu receptors be evoked by high-frequency stimulation. Immunohistochemical studies have demonstrated that early in postnatal development in the cerebral cortex, group I mGlu receptors are excluded from the main body of the postsynaptic specialization (Fig. 4). Its highest concentration occurs at the edge of the postsynaptic specialization (termed perisynaptic location), as well as along the extrasynaptic plasma membrane (López-Bendito et al., 2002a; Fig. 4). A similar distribution for $mGlu_1$ and $mGlu_5$ is seen in the adult (Luján et al., 1996, 1997; López-Bendito et al., 2002a). In the cerebellum, however, $mGlu_1$ is already present in Purkinje cell spines before the arrival of excitatory synapses, and as development progresses, $mGlu_1$ accumulates in perisynaptic positions, in association with the maturation of parallel fiber-Purkinje cell synapses (López-Bendito et al., 2001).

The acquisition of group II and III mGlu receptors at synapses is unexplored. We mainly know their final localization in the adulthood. Here, group II mGlu receptors, $mGlu_2$ and $mGlu_3$, can be found both at postsynaptic and presynaptic sites (Fig. 4), depending on the

brain region and cell type. At their postsynaptic location, $mGlu_2$ is preferentially located outside the synapse (Luján et al., 1997). In contrast, $mGlu_3$ is found to be associated with glutamatergic synapses, including the postsynaptic specialization, and glial cells (Tamaru et al., 2001; Fig. 4). At presynaptic locations, $mGlu_2$ and $mGlu_3$ are concentrated in the pre-terminal portion of axons or along the extrasynaptic membrane of axon terminals, and always outside the presynaptic active zone (Luján et al., 1997; Shigemoto et al., 1997; Tamaru et al., 2001; Fig. 4). Regarding group III mGlu receptors, $mGlu_4$, $mGlu_7$ and $mGlu_8$ are mainly concentrated along the presynaptic active zone of glutamatergic (Shigemoto et al., 1996, 1997; Kinoshita et al., 1998; Corti et al., 2002; Dalezios et al., 2002; Somogyi et al., 2003) and GABAergic synapses (Corti et al., 2002; Dalezios et al., 2002; Somogyi et al., 2003; Fig. 4), where they may act as auto- and heteroreceptors, respectively. No information is as yet available about the factors that control this differential targeting to different subcellular domains or their recruitment in inhibitory synapses during development.

GABAergic synapses. The involvement of $GABA_A$ receptors in the construction of postsynaptic domains of inhibitory synapses is not fully known. $GABA_A$ receptors are concentrated at synapses opposite to GABA releasing terminals (Fig. 4), but receptor complexes containing only α- and β-subunits form channels that are inserted in the plasma membrane (Gunther et al., 1995). While the γ subunits are not necessary for receptor assembly and translocation to the neuronal surface, they seem to be required for clustering of postsynaptic $GABA_A$ receptor subtypes (Essrich et al., 1998; Schweizer et al., 2003). $GABA_A$ receptor subunits are also located along the extrasynaptic plasma membrane of neurons (Fig. 4), generally at low densities (Nusser et al., 1995), although the δ subunit is localized exclusively at extrasynaptic sites (Nusser et al., 1998a; Fig. 4). Furthermore, some $GABA_A$ receptor subunits (e.g. the α6, β2/3 and γ2 subunits) have also been found at glutamatergic synapses (Nusser et al., 1996, 1998a).

No information is as yet available about the acquisition of $GABA_B$ receptors at synapses. They show, however, one of the most intriguing locations of all neurotransmitter receptors during postnatal development and adulthood. Electrophysiological, pharmacological and immunohistochemical studies have identified $GABA_B$ receptors on postsynaptic sites and on presynaptic GABAergic and glutamatergic axons (Misgeld et al., 1995). Early in postnatal development, $GABA_B$ receptors are located at extrasynaptic and perisynaptic sites, as well as at pre- and postsynaptic sites, similarly to the distribution observed in the adulthood (López-Bendito et al., 2002b; Panzanelli et al., 2004; Fig. 4). They are abundant on dendritic spines postsynaptic to glutamatergic axon terminals in the brain (Fritschy et al., 1999; Gonchar et al., 2001; López-Bendito et al., 2002b, 2004b; Kulik et al., 2002, 2003; Luján et al., 2004) and on the postsynaptic specialization (Billinton et al., 2001; Gonchar et al., 2001; Kulik et al., 2002). In contrast, $GABA_B$ receptors are rarely associated with synapses opposite to GABA releasing terminals (López-Bendito et al., 2002b, 2004b; Kulik et al., 2002, 2003; Luján et al., 2004).

At their presynaptic location, $GABA_B$ receptors are found in the preterminal portion of axons, in the extrasynaptic membrane of axon terminals and in presynaptic active zones of glutamatergic and GABAergic synapses (López-Bendito et al., 2002b; Kulik et al., 2002, 2003; Luján et al., 2004; Fig. 4), where they likely act as hetero- and autoreceptors, respectively.

Concluding remarks

A combination of electrophysiological, molecular, *in situ* hybridization and immunohistochemical techniques has begun to shed light on the role and distribution of neurotransmitter receptors in the developing brain. This review illuminates recent evidence showing how glutamate and GABA receptors exert different roles during primary nervous structure establishment prior to the emergence of their role in neurotransmission. In this way, the early activation of glutamate and GABA receptor subunits, expressed by several kinds of cells, appears to account for the regulation of proliferation, migration and differentiation during CNS development. Additionally, early expression of the receptor subunits accounts for their involvement in the establishment of synaptic contact and the refinement of neuronal circuits. Moreover, changes in the level of expression and distribution of neurotransmitter receptors are critical steps in normal synapse development, and abnormalities in these processes may be responsible for neural diseases. Which specific changes are critical to both normal development and disease processes remain to be defined. This may not be particularly easy because the molecular composition and functional properties of synapses are heterogeneous. Indeed, glutamate and GABA receptors can be targeted during synaptogenesis to any subcellular compartment of the neuronal surface, in a receptor subunit- and cell type-dependent manner. Presumably, the different neurotransmitter receptor subunits are targeted to specific subcellular compartments because their intrinsic properties are most suited for the physiological functions at those sites during development and in the adulthood. Continued identification of the molecular components of individual synapses promises to offer new insights on the mechanisms that control synaptogenesis processes and the signaling between neurons in the developing brain. A more complete understanding of the roles of the many neurotransmitter receptor subunits described in this review, and of the functional interaction with other signaling proteins, should provide an increasing understanding of brain development and neurological diseases.

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