Neuroscience 130 (2005) 567–580

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-

0306-4522/05$30.00+0.00
doi:10.1016/j.neuroscience.2004.09.042

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