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REVIEW

Neurexins and neuroligins: new partners for $GABA_A$ receptors at synapses

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Abstract **Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain. As one of several types of endogenous receptors, $GABA_A$ receptors have been shown to be essential in most, if not all, aspects of brain functioning, including neural development and information processing. Mutations in genes encoding $GABA_A$ receptors and alterations in the function of $GABA_A$ receptors are associated with many neurologic diseases, and $GABA_A$ receptors have been clinically targeted by many drugs, such as benzodiazepines and general anesthetics. Extensive studies have revealed a number of intracellular chaperons/interactions for $GABA_A$ receptors, providing a protein–protein network in regulating the trafficking and location of $GABA_A$ receptors in the brain. Recently, neurexins and neuroligins, two families of transmembrane proteins present at neurological synapses, are implicated as new partners to $GABA_A$ receptors. These works shed new light on the synaptic regulation of $GABA_A$ receptor activity. Here, we summarized the proteins that were implicated in the function of $GABA_A$ receptors, including neurexins and neuroligins.**

Keywords $GABA_A$ receptors, synapses, neurexins, neuroligins

Introduction

Gamma-aminobutyric acid (GABA) was first identified in the central nervous system in 1950 (Roberts and Frankel, 1950). Since then, GABA has been proven to be the major inhibitory neurotransmitter in the brain of vertebrates. Three endogenous GABA receptors have been identified: ionotropic $GABA_A$, $GABA_C$ receptors, and metabotropic $GABA_B$ receptors. $GABA_A$ receptors are pentameric ion channels that are permeable to chloride ions and HCO_3^-. $GABA_A$ receptors express ubiquitously throughout the brain, serving as the major inhibition system to maintain the balance of the neural network. It is not surprising that $GABA_A$ receptors are important in nearly all brain functions including anxiety and depression, learning and memory, cognition, etc. Alteration of $GABA_A$ receptor function is the cause of many neurologic diseases. For example, anxiety disorders have been largely, if not entirely, attributed to impaired GABAergic inhibition (Nutt and Malizia, 2001), and drugs that enhanced the opening of $GABA_A$ receptors (e.g., benzodiazepines) have been widely used to treatment these disorders (Rupprecht et al., 2006). Mutations and deletions in genes encoding the $GABA_A$ receptors have been reported in Epilepsy (Baulac et al., 2001; Wallace et al., 2001; Cossette et al., 2002; Kananura et al., 2002), sleeping disorders (Buhr et al., 2002), autism spectrum disorders (Collins et al., 2006), Angelman syndrome (Dan and Boyd, 2003) and schizophrenia (Petryshen et al., 2005). In most circumstances, $GABA_A$ receptors mediate fast neuronal hyperpolarization upon activation, thus causing brain inhibition, and serve to fine-tune the maintenance of excitation/inhibition balance in the brain. However, during early development, activation of $GABA_A$ receptors depolarizes/excites the neurons, due to the lack of K^+-Cl^- cotransporter 2 (KCC2) expression causing higher

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chloride concentration inside the neurons (Cherubini et al., 1991; Rivera et al., 1999).

Native $GABA_A$ receptors are comprise of five subunits from eight distinct subunit families including α1-6, β1-3, γ1-3, δ, ε, θ, π and ρ1-3 (Sieghart et al., 1999; Whiting, 1999). Various subunits express in the brain with different distribution and abundance. The α1 subunit is the most abundant subunit found in the brain. In addition to the α1 subunit, β1-3 subunits and γ2 subunits are also expressed throughout the brain, while other subunits are more restricted to certain brain areas and neuron populations (Pirker et al., 2000). Existing evidence suggests that the major $GABA_A$ receptors in the brain are comprised of different α and β subunits, with one γ2 subunit (Sieghart and Sperk, 2002; Lüscher and Keller, 2004). Subunit composition both determines the biophysical and pharmacological features of the $GABA_A$ receptors and affects the receptor location and the activation manners. For example: the $GABA_A$ receptors containing α1-3, with a γ2 subunit, mainly localize at the synapses (Nusser et al., 1995, 1998; Fritschy et al., 1998; Brünig et al., 2002); the receptors containing α4 or α6 subunits, together with a δ subunit (replacing the γ subunit from the $GABA_A$ receptor complex), are found to be excluded from the postsynaptic sites in cerebellar granule cells (Nusser et al., 1998) and hippocampal dentate gyrus granule neurons (Wei et al., 2003); receptors containing the α5 subunit are also shown to be predominately located at the extrasynaptic sites and are thought to be activated by spillover of synaptic-releasing GABA to mediate the tonic inhibition in the brain (Caraiscos et al., 2004).

The $GABA_A$ receptors belong to cysteine-loop receptor superfamily, which is also comprised of acetylcholine, glycine and $5\text{-}HT_3$ receptors (Cockcroft et al., 1990; Lester et al., 2004). All $GABA_A$ receptor subunits share a similar domain structure including a large extracellular N-terminal domain (NTD), four transmembrane domains (TM1-4), and a relatively short extracellular C-terminal fragment (CTF). The signature two cysteines form a disulfide bond in a loop of 13 residues within the large NTD (Connolly and Wafford, 2004). The TM2 helix from each subunit forms the ion channel pore (Absalom et al., 2009; Cederholm et al., 2009). Site-directed mutagenesis studies show that GABA binds to $GABA_A$ receptors at the interface between α and β subunit; benzodiazepines (an important class of psychoactive drugs acting on the $GABA_A$ receptor) bind to $GABA_A$ receptors at the interface between α and γ2 subunit (Smith and Olsen, 1995; Sieghart and Sperk, 2002). These observations have been further confirmed by the comparative modeling studies (Ernst et al., 2003, 2005) based on the structure of acetylcholine binding protein (Brejc et al., 2001) and acetylcholine receptors (Miyazawa et al., 2003; Unwin, 2005).

Given the pathophysiological and therapeutic importance of these receptors, extensive studies have been conducted to look for the endogenous chaperons/partners for $GABA_A$ receptors and to assess the functional implication of these complexes. In this article we reviewed the proteins that have been implicated in the function of $GABA_A$ receptors, including the two newly-identified membrane protein families: neurexins and neuroligins.

The cytoplasmic proteins implicated in $GABA_A$ receptor functions

Gephyrin

Gephyrin was first identified as a postsynaptic scaffold protein that interacts physically and functionally with glycine receptors (Pfeiffer et al., 1982; Prior et al., 1992). Gephyrin is a 93-KDa protein, expressed throughout the central nervous system and subjected to alternative splicing (Prior et al., 1992; Paarmann et al., 2006). A high degree of colocalization of gephyrin and $GABA_A$ receptors subunits (γ2, α1, α2, et al.) have been demonstrated in the GABAergic synapses by light microscopy (Essrich et al., 1998; Giustetto et al., 1998; Sassoè-Pognetto et al., 2000; Christie et al., 2002) and electron microscopy techniques (Todd et al., 1996; Giustetto et al., 1998; Christie et al., 2002). However, as of yet no direct binding has been found between gephyrin and $GABA_A$ receptors. Functional analysis revealed that gephyrin plays an important role in the synaptic localization and clustering of postsynaptic $GABA_A$ receptors, even though postsynaptic accumulation of $GABA_A$ receptors under certain conditions can still occur independently of gephyrin (Alldred et al., 2005). Inactivation of gephyrin expression, using RNAi knockdown, reduces the receptor cluster and increases the diffusion rate of postsynaptic $GABA_A$ receptors (Jacob et al., 2005). Knockout gephyrin in the neurons drastically reduces the number and size of postsynaptic $GABA_A$ receptor clusters and GABAergic synaptic transmission (Essrich et al., 1998; Baer et al., 1999; Kneussel et al., 1999; Fischer et al., 2000). As a putatively postsynaptic scaffold protein of inhibitory synapses, gephyrin binds to tubulin and microtubules (Kirsch et al., 1991; Kirsch and Betz, 1995) as well as several cytoskeleton-related proteins, such as profolin and Mena (Mammoto et al., 1998; Giesemann et al., 2003) and dynein light chain 1 and 2 (Fuhrmann et al., 2002). However, disruption of cytoskeleton (including actin and microtubules) and extracting soluble proteins with Triton have no effect on the clustering of postsynaptic gephyrin and $GABA_A$ receptors in the inhibitory synapses (Allison et al., 2000), even though microtubule depolymerization was shown to affect certain function of $GABA_A$ receptors (Whatley et al., 1994). Thus, the synaptic function of gephyrin interacting with cytoskeleton and cytoskeleton-related proteins remains unclear.

$GABA_A$ receptor associated protein

$GABA_A$ receptor associated protein (GABARAP) was identified in a yeast two-hybridization screening in which the intracellular loop of $GABA_A$ receptor γ2 subunit was used

as the bait (Wang et al., 1999). GABARAP is a 16 kDa protein, which is highly conservative in eukaryotic cells. Mammalian GABARAP (human, bovine, rat and mouse) displays 100% identity in amino acid sequences. GABARAP belongs to an ubiquitin-like protein superfamily that is implicated in intracellular protein trafficking (Wang et al., 1999; Tanida et al., 2004). The interaction was found to be mediated between GABARAP residues 36–68 and γ subunits (Nymann-Andersen et al., 2002a). Further analysis shows that this interaction is restricted to γ1-3 subunits, not to other $GABA_A$ receptor subunits (Nymann-Andersen et al., 2002b). In humans and mice, GABARAP expresses, not restricted to the brain, but widely in different tissues including heart, liver and skeletal muscles (Xin et al., 2001). Imaging studies in the cultured neurons showed that the majority of GABARAP localized in the endoplasmic reticulum and Golgi, co-localizing with $GABA_A$ receptors inside the cell but not at the postsynaptic surface (Leil et al., 2004). Using both heterologous and neuronal culture systems, overexpression of GABARAP was shown to increase the surface expression of $GABA_A$ receptors and affect GABA-induced membrane currents (Chen et al., 2000, Boileau et al., 2005; Chen et al., 2005). Furthermore, the GABARAP was shown to interact with gephyrin using *in vitro* assay (Kneussel et al., 2000). However, the GABARAP knockout mice show normal $GABA_A$ receptors function and synaptic clustering of $GABA_A$ receptors γ2 subunit and gephyrin (O'Sullivan et al., 2005). Conversely, the gephyrin deficient mice show normal GABARAP expression but with a significant alteration in the synaptic clustering of $GABA_A$ receptor γ2 subunit (Kneussel et al., 2000). These observations argue against a function of GABARAP in the synaptic targeting of postsynaptic $GABA_A$ receptors. Thus, GABARAP seems to function as a traffic factor of intracellular $GABA_A$ receptors and is dispensable for the clustering of postsynaptic $GABA_A$ receptors.

Other proteins implicated in $GABA_A$ receptor functions

Besides the extensive research on gephyrin and GABARAP, many $GABA_A$ receptors-associated proteins have been identified. For example, the N-ethylmaleimide-sensitive factor (Goto et al., 2005), Plic-1 (also interacts with α-subunit) (Bedford et al., 2001), and the brefeldin A-inhibited GDP/GTP exchanger factor 2 (Charych et al., 2004) are all shown to interact with the $GABA_A$ receptors β-subunit and regulate the membrane delivery of ER-exported $GABA_A$ receptors. The clathrin adaptor AP-2 (Kittler et al., 2000; Vithlani and Moss, 2009), and the huntingtin-associated protein 1 (Kittler et al., 2004; Twelvetrees et al., 2010) and $GABA_A$ receptors interacting factor-1 (Beck et al., 2002; Smith et al., 2006), bind to the $GABA_A$ receptors β-subunit and regulate the internalization and recycling of $GABA_A$ receptors. The physiologic role of these interactions in the regulation of synaptic $GABA_A$ receptors must still be further explored.

The plasma membrane proteins implicated in $GABA_A$ receptor functions: neurexins and neuroligins

An introduction to neurexins and neuroligins

Neurexins and neuroligins are both synaptic adhesion molecules. Neurexins were first identified as alpha-latrotoxin receptors (Ushkaryov et al., 1992). In vertebrates, like in humans and mice, three neurexin genes (n*eurexin-1*, *-2* and *-3*) exist, each encoding a α- and β-form of neurexin (Neurexin-1α, -2α, -3α and Neurexin-1β, -2β, -3β, respectively) from two distinct promoters (Tabuchi and Südhof, 2002). Neurexins are neuron-specific proteins that undergo extensive alternative splicing, and which could potentially have more than 1000 isoforms in the brain (Missler et al., 1998). Extensive functional analysis and antibody labeling studies suggest that neurexins localize in the presynaptic terminals of synapses (reviewed in Dean and Dresbach, 2006; Lisé and El-Husseini, 2006; Craig and Kang, 2007; Südhof, 2008). However, the precise synaptic location (especially presynaptic versus postsynaptic) still requires a high-affinity antibody enabling ultrastructure analysis. Neuroligins (1–4) are the high affinity ligands of neurexins (Ichtchenko et al., 1995; Südhof, 2008). Like neurexins, neuroligins are Type-1 transmembrane proteins. All neuroligins are postsynaptic localized. Among these, neuroligin-1 expressed exclusively in the excitatory synapses (Song et al., 1999), while neuroligins-2 expressed in the inhibitory synapses (Varoqueaux et al., 2004). All neuroligins bind to neurexins with the affinity ranging from nanomolar to micromolar depending on the isoforms and alternative splicing of both proteins (Ichtchenko et al., 1996; Nguyen and Südhof, 1997; Boucard et al., 2005; Araç et al., 2007).

In vitro studies suggest that neurexins and neuroligins are candidates implicated in synapse formation. Using the artificial synapses-formation assay, which was developed to identify the minimum protein set required for synapse formation *in vitro*, expressing neuroligins in non-neuronal cells has been shown to induce presynaptic differentiation in the neurons at the contacting sites (Scheiffele et al., 2000; Chubykin et al., 2005). Conversely, neurexins alone have been shown to be sufficient to induce postsynaptic differentiations, including aggregation of synaptic scaffold proteins and postsynaptic receptors in the same assay (Dean et al., 2003; Graf et al., 2004). Expressing neuroligins in neurons also increases the number of synapses (Chubykin et al., 2007). However, due to the fact that: a) the synapses formation is normal, and b) the synapses maturation is severely impaired, in both triple neurexin-α (Missler et al., 2003; Dudanova et al., 2007) and triple neuroligins (1, 2 and 3) knockout mice (Varoqueaux et al., 2006), it seems more likely that the participation of neurexins and neuroligins would occur in the synapse development stage rather than during the synapse formation process.

Neurexins and $GABA_A$ receptors

Recently, the extracellular domain of neurexins was found to directly interact with N-terminal domain of $GABA_A$ receptor α1 subunit, with a 2 μmol/L affinity, using surface plasmon resonance measurements (Zhang et al., 2010). This interaction is not dependent upon external calcium concentration and neurexin splicing site 4, which is reported to be essential for most other interactions with neurexins. *In vitro* pull-down assay shows that neurexins simultaneously bind to the $GABA_A$ receptor and neuroligin-1. Interestingly, overexpression of neurexins in the non-neuronal (HEK293) cells expressing $GABA_A$ receptors (α1β2γ2) reduced both the GABA-induced whole-cell current and the protein level of $GABA_A$ receptors. This suggests a function of neurexins in regulating surface $GABA_A$ receptors. The functional implication of this interaction has been further explored in cultured neurons. Imaging analysis showed that overexpression of neurexins in cultured hippocampal neurons reduced the protein level, but not the number of postsynaptic α1-containing $GABA_A$ receptors. In cultured neurons, neurexin overexpression and bath application of recombinant protein containing the neurexins extracellular domain impaired action-potential (AP)-induced GABAergic synaptic transmission, left the glutamergic synaptic transmission intact. All the neurexins isoforms (1-, 2-, 3β and 1α) that were tested are active. This functional effect is mediated via an extracellular mechanism on the neuronal surface, because a mutant neurexin, which was trapped in ER by fusing with an ER-retention signal, has no effect on GABAergic synaptic transmission. Thus, these observations show that neurexins interact with postsynaptic $GABA_A$ receptors to directly affect AP-induced GABAergic synaptic transmission.

These new findings raise several interesting issues. First of all, the overexpression of neurexins reduces the concentration of postsynaptic $GABA_A$ receptors, but has no effect on the amplitude of miniature inhibitory postsynaptic synaptic currents (mIPSC). This seems to be surprising because mIPSC amplitude is thought to reflect the number of postsynaptic $GABA_A$ receptors. However, numerous recent studies suggest that miniature postsynaptic synaptic currents (minis) are more complex than was previously thought. Decreases in postsynaptic $GABA_A$ receptors, induced by the knockout of specific $GABA_A$ receptor subunits, do not always cause a significant decrease in mIPSCs amplitude (Goldstein et al., 2002; Ortinski et al., 2004; Herd et al., 2008). Furthermore, minis have been shown to be recruited from a non-standard vesicle pool, as opposed to the standard pool, for AP-induced synaptic transmission (Atasoy et al., 2008; Fredj and Burrone, 2009). Moreover, dissociation between mini frequency and release probability and synapse numbers has been previously observed (Maximov et al., 2009; Xu et al., 2009; Zhang et al., 2009). Therefore, the "mini paradox" here seems more apparent than real and might represent a distinct mechanism of $GABA_A$ receptor modulation in the spontaneous synaptic transmission. Second, it remains unclear as to whether or not this $GABA_A$ receptors-neurexins interaction is brought about in a cis- or trans-interaction manner. Neurexins are primarily presynaptic localized, but postsynaptic localization is also been reported (Taniguchi et al., 2007). Furthermore, certain alternative splicing events in neurexins would generate truncated forms of neurexins as secreted factors (Taniguchi et al., 2007). Thus, the identification of the precise timing and source of neurexins that bind to $GABA_A$ receptors will help researchers better understand the sequential cascade of synaptic events during synapse formation and maturation. Ultimately, Zhang et al. (2010) examined the physiologic relevance of neurexins-$GABA_A$ receptor interaction primarily using gain-of-function assay. Further studies using loss-of-function assay are essential in validating the *in-vivo* function of this interaction, albeit gene deletion of all six neurexins in mice is technically challenging.

From the viewpoint of human diseases, neurexins-$GABA_A$ receptors interaction seems physiologic meaningful in cognitive diseases, such as autism spectrum disorders (ASD) and schizophrenia. Changes in neurexin-1 gene (NRXN1), including point mutations and copy number variations, have been found in ASD (Szatmari et al., 2007; Kim et al., 2008; Marshall et al., 2008; Zahir et al., 2008; Yan et al., 2008; Bucan et al., 2009; Wiśniowiecka-Kowalnik et al., 2010) and schizophrenia patients (Kirov et al., 2008; Walsh et al., 2008; Need et al., 2009; Rujescu et al., 2009; Shah et al., 2010). Interestingly, deficits in brain GABA systems and mutations in genes expressing $GABA_A$ receptors subunits are thought to associate with, or lead to, the pathogenesis of ASD (reviewed in Dykens et al., 2004; Blatt, 2005; Schmitz et al., 2005; Lalande and Calciano, 2007; Solís-Añez et al., 2007) and schizophrenia (reviewed in Guidotti et al., 2005; Uhlhaas and Singer, 2010; Cherlyn et al., 2010; Gonzalez-Burgos et al., 2010). Thus, the observation of direct interaction between neurexins and $GABA_A$ receptors supports the idea that deficits in GABAergic synapses are risk factors in causing these cognitive diseases. Further characterization of the pathophysiology of this interaction will help researchers better understand these diseases.

Neuroligins and $GABA_A$ receptor functions

Although no direct binding between neuroligins and $GABA_A$ receptors has been reported, Poulopoulos et al. (2009) reported the existence of a triplex of neuroligins-2 with gephyrin and collybistin, in an attempt to look for the protein interacting with the cytoplasmic tail of neuroligin-2 using the yeast two-hybridization technique (Poulopoulos et al., 2009). All neuroligins bind to the E-domain of gephyrin through a 15-amino acid motif, which is conservative among all

neuroligins. Among the neuroligins family, only neuroligins-2 binds and activates collybistin, a protein that recruits gephyrin to the postsynaptic sites in its active form (Kins et al., 2000; Harvey et al., 2004). By itself, overexpression gephyrin does not recruit the $GABA_A$ receptor in non-neuronal cells (Meyer et al., 1995). However, coexpressing neuroligins-2 and collybistin together with gephyrin is sufficient to recruit $GABA_A$ receptors in COS7 cells. In support of the physiologic importance of this neuroligins-2, gephyrin and collybistin triplex at GABAergic synapses, knockout neuroligins-2 reduced the number of postsynaptic gephyrin clusters at the inhibitory synapses formed on the soma, but not at the dendrites of the neurons. The synaptic strength of inhibitory synapses is impaired in neuroligins-2 null neurons (Varoqueaux et al., 2006; Hoon et al., 2009; Gibson et al., 2009; Poulopoulos et al., 2009), but that of the excitatory synapses is not impaired. Consistently, collybistin-deficient mice show impaired clustering of the postsynaptic gephyrin and $GABA_A$ receptors and reduced GABAergic synaptic transmission (Papadopoulos et al., 2007). Thus, these observations suggest that neuroligins-2 regulates the synaptic targeting of $GABA_A$ receptors via interaction with gephyrin and collybistin.

Perspectives

$GABA_A$ receptors are one of the major neurotransmitter receptors in the brain. Activation of $GABA_A$ receptors functions as the coordinator in the neural network to maintain brain harmony. Extensive studies have led to the identification of the many $GABA_A$ receptors-associated proteins that regulate the trafficking, posttranslational modulation, synaptic targeting and function of $GABA_A$ receptors. As described above, with the exception of neurexins, most of the known $GABA_A$ receptors-associated proteins bind to the intracellular loops of $GABA_A$ receptors subunits. Neurexins are synaptic proteins that are ubiquitously expressed in the brain and bind to the $GABA_A$ receptors extracellular domains. In view of the nature of $GABA_A$ receptors as membrane proteins, and knowing that the extracellular part of $GABA_A$ receptors represents $> 50\%$ amino acid residues in the total protein, it is reasonable to speculate that extracellular binding partners of $GABA_A$ receptors would play a more important role than expected in the synaptic targeting of $GABA_A$ receptors and signaling transduction at the GABAergic synapses. Thus, an investigation of the extracellular protein network surrounding $GABA_A$ receptors would be an interesting research direction to pursue in the future.

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