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GABA Type A Receptor Trafficking and the Architecture of Synaptic Inhibition

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Abstract

Ubiquitous expression of GABA type A receptors ($GABA_AR$) in the central nervous system establishes their central role in coordinating most aspects of neural function and development. Dysregulation of GABAergic neurotransmission manifests in a number of human health disorders and conditions that in certain cases can be alleviated by drugs targeting these receptors. Precise changes in the quantity or activity of $GABA_ARs$ localized at the cell surface and at GABAergic postsynaptic sites directly impact the strength of inhibition. The molecular mechanisms constituting receptor trafficking to and from these compartments therefore dictate the efficacy of $GABA_AR$ function. Here we review the current understanding of how $GABA_ARs$ traffic through biogenesis, plasma membrane transport, and degradation. Emphasis is placed on discussing novel GABAergic synaptic proteins, receptor and scaffolding posttranslational modifications, activity-dependent changes in $GABA_AR$ confinement, and neuropeptide and neurosteroid mediated changes. We further highlight modern techniques currently advancing the knowledge of $GABA_AR$ trafficking and clinically relevant neurodeve lopmental diseases connected to GABAergic dysfunction.

Keywords

$GABA_AR$; trafficking; synapse; inhibition; plasticity

INTRODUCTION

$GABA_A$ receptors ($GABA_ARs$) are ligand-gated ionotropic chloride (Cl^-) channels responsible for most fast inhibitory neurotransmission in the mature central nervous system (CNS). Ubiquitous expression supports their central role in regulating most aspects of CNS function. Clinically, these receptors are important drug targets for anti-convulsant, anxiolytic, and sedative-hypnotic agents including benzodiazepines (BZs), barbiturates, alcohol, certain anesthetics and neurosteroids. Underlying deficits in GABAergic neurotransmission occur in a wide variety of neurological disorders such as epilepsy, psychiatric disorders (anxiety [Mohler, 2012; Nuss, 2015], depression [Luscher et al., 2011b; Pehrson and Sanchez, 2015], post-traumatic stress disorder [Pitman et al., 2012; Moller et al., 2016; Trousselard et al., 2016; Bandelow et al., 2017]) and

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neurodevelopmental disorders including autism (Robertson et al., 2016; Chao et al., 2010; Coghlan et al., 2012), Fragile X (Lozano et al., 2015; Wang et al., 2015) and schizophrenia (Gonzalez-Burgos et al., 2010; Bristow et al., 2015; Wijtenburg et al., 2015). Importantly, pathophysiological events including seizures (Scharfman and Brooks-Kayal, 2014), ischemic stroke (Carmichael, 2012; Blicher et al., 2015; Wu and Sun, 2015), traumatic brain injury (Guerriero et al., 2015) and stress can cause adaptive changes in $GABA_AR$ neurotransmission, compromising GABAergic inhibition and further hampering recovery.

Binding of the neurotransmitter GABA induces $GABA_AR$ ion channel opening, $C1^-$ influx, and subsequent membrane hyperpolarization (Fig. 1A). These receptors are heteropentameric structures typically composed of two α (α1–6), two β (β1–3), and either a γ (γ1–3) or a δ subunit (Olsen and Sieghart, 2009). The most common $GABA_ARs$ providing fast synaptic inhibition in the mature mammalian cerebral cortex contain $\alpha1\beta2\gamma2$ subunits (Fig. 1A,B) (Sieghart, 2006). Despite the great diversity of $GABA_AR$ subunits (α1–6, β1–3, γ1–3, δ, ε, θ, π, ρl–3) and possible configurations, these receptors produce two types of currents: synaptic (phasic) and tonic. Presynaptic terminal release of GABA onto post-synaptically clustered $GABA_ARs$ triggers fast, transient synaptic currents, while ambient “spill over” GABA generates a persistent tonic current via activation of high affinity, low conductance extrasynaptic receptors. $GABA_AR$ subunit composition therefore determines receptor cell surface localization, electrophysiological properties and drug sensitivities.

Receptors containing α1–α3 subunits are primarily located at GABAergic synapses via direct association with gephyrin (Tretter et al., 2008, 20ll; Mukherjee et al., 2011), the key GABAergic and glycinergic postsynaptic scaffolding protein (Essrich et al., l998; Schweizer et al., 2003; Triller and Choquet, 2005; Jacob et al., 2008; Luscher et al., 2011a). The $\gamma2$ subunit is required for maintenance of most synaptic receptors and gephyrin (Essrich et al., l998; Schweizer et al., 2003). In addition, recent identification of the $GABA_AR$ regulatory Lhfpl (GARLH) family as putative $GABA_AR$ auxiliary subunits indicates the $\gamma2$ subunit is central in formation of a native tripartite complex between receptors, GARLH protein LH4 and the postsynaptic cell adhesion protein neuroligin 2 (NL2) (Yamasaki et al. 2017). Although predominantly clustered at synapses, $\gamma2$-containing receptors are also found at extrasynaptic sites and contribute to tonic current that is sensitive to positive allosteric modulation by the benzodiazepine drug class (Preno-sil et al., 2006). Receptors containing δ, a4 or a6 subunits do not interact with gephyrin, leading to their extrasynaptic localization and contribution to tonic benzodiazepine-insensitive $GABA_AR$ currents (Glykys and Mody, 2007a; Lee and Maguire, 2014). The a5 subunit can contribute to both modes of $GABA_AR$ signaling as it can directly interact with gephyrin synaptically (Brady and Jacob, 2015) and extrasynaptically with the actin binding protein radixin, a member of the ezrin/radixin/moesin (ERM) family (Loebrich et al., 2006). Although synaptic and extrasynaptic receptors are often described as distinct entities, single molecule tracking, electrophysiological, biochemical, and other imaging-based methods have revealed that receptors in both populations diffuse continually in the plasma membrane, with enhanced accumulation of synaptic receptors depending primarily on interactions between gephyrin and $GABA_ARs$ (Fig. 2).

In addition to their inhibitory function in the mature CNS, $GABA_A$Rs are of fundamental importance in organization of newly forming circuits by promoting dendritic outgrowth and synaptogenesis. Synapses develop first with the emergence of excitatory GABAergic synaptic signals that drive the subsequent establishment of glutamatergic synapses, before GABA neurotransmission shifts to functioning as an inhibitory signal (Ben-Ari et al., 2007; Deng et al., 2007; Cellot and Cherubini, 2013). The polarity of $GABA_A$R neurotransmission (inhibitory or excitatory) depends on the intracellular chloride concentration ($[Cl^-]_i$) set by the activity of two cationchloride transporters: Cl^- importer Na-K-Cl^- cotransporter (NKCC1) and neuronal Cl^- extruder K +-Cl^- cotransporter (KCC2). NKCC1 function predominates in early brain development generating a Cl^- reversal potential $\left(E_{Cl}^{-}\right)$ more positive than the membrane potential (V_m), leading to Cl^- efflux and depolarization when the $GABA_A$R opens. As development proceeds, KCC2 expression increases, resulting in lower Cl^- levels inside neurons and inhibitory $GABA_A$R signaling via Cl^- influx (Farrant and Kaila, 2007; Galanopoulou, 2008). Therefore, the functional outcome of altering GABAergic activity is highly dependent on chloride homeostasis. In addition, E_{GABA} is similarly regulated in neural differentiation of adult born neurons in the hippocampus and olfactory bulb (reviewed in Lledo et al., 2006; Markwardt and Overstreet-Wadiche, 2008). Furthermore, pathological injury and disease states including seizures, ischemic stroke and traumatic brain injury can modulate E_{GABA} (reviewed in Loscher et al., 2013).

In simplified terms, the strength of phasic and tonic $GABA_A$R neurotransmission is determined by surface receptor levels, although receptor clustering at synapses by key scaffolding protein interactions is essential for phasic $GABA_A$R signaling (Jacob et al., 2008; Luscher et al., 2011a). Here we discuss cellular mechanisms modulating $GABA_A$R intracellular trafficking, surface levels, and localization during constitutive and abnormal conditions, thus providing key information about the dynamic calibration of $GABA_A$R neurotransmission.

$GABA_A$R ASSEMBLYAND FORWARD TRAFFICKING

$GABA_A$R biogenesis is controlled via regulated assembly of subunits into heteropentamers within the endoplasmic reticulum (ER). Due to the diversity of receptors generated in recombinant systems during multiple independent subunit transfections, studies on assembly of concatenated subunit constructs have been a major route for determining receptor configuration. As viewed from outside the cell, the $\alpha 1\beta 2\gamma 2$ $GABA_A$R subtype indicates a counterclockwise subunit configuration of γ-β-α-β-α (Fig. 1B) (Minier and Sigel, 2004; Baur et al., 2006). $GABA_A$R studies using heterologous cells show that a β subunit is required for receptor cell surface expression, while the $\alpha\beta$ interface that forms the GABA-binding site is required for functional responses. Although unlikely to occur *in vivo,* βl or ß3 homomeric channels form, while other individual subunit expression leads to ER retention (Krishek et al., 1996; Wooltorton et al., 1997). Co-expression of $\gamma 2$ subunits with $\alpha\beta$ leads to preferential assembly of $\alpha\beta\gamma 2$ receptors (Draguhn et al., 1990; Angelotti and Macdonald, 1993). Receptor complex formation begins with $\alpha\beta$ heterodimer formation, with the N-terminal domains controlling this process. Several high-resolution structural studies of pentameric ligand-gated ion channels, including the recently solved human $\beta 3$ $GABA_A$R

homopentamer informs our understanding of the receptor (Miller and Aricescu, 2014). Each individual subunit has a large N-terminal extracellular domain (ECD) followed by four transmembrane domains (TM1-TM4) and a short extracellular C terminus (Fig. 1C). The TM2 of each subunit contributes to the formation of the receptor ion channel pore, where the large intracellular loop between TM3 and TM4 is important for protein interactions and phosphorylation-dependent regulation. The ECD (ER luminal during receptor assembly) is comprised of an N-terminal α-helix followed by a core β sandwich of 10 β strands, with the GABA-binding site near the ECD midpoint. Studies of a $\alpha1\beta2\gamma$ recombinant receptors demonstrate that the N-terminal putative α helical region of the $\alpha1$ subunit is critical for surface receptor expression, while deletion of the other subunits N-terminal extensions had minimal effects on surface expression (Wong et al., 2015). Rather, deletion of the $\beta2$ α-helix decreased GABA sensitivity and receptor desensitization, while $\gamma2$ N-terminal deletions reduced incorporation of $\gamma2$ in receptors. ER chaperones including calnexin and binding immunoglobulin protein (BiP/Grp78) contribute to receptor assembly (Fig. 2) (Connolly et al., 1996; Bradley et al., 2008), facilitating maturation of the $\alpha1$ subunit (Di et al., 2013) in a glycan-dependent and independent manner. Recent findings suggest GABA can function as an intracellular chaperone for both recombinant (Eshaq et al., 2010) and endogenous receptors, as enhanced intracellular GABA levels promotes receptor forward trafficking and exocytosis in neurons (Wang et al., 2015). In support of this finding, immunogold labeling of rodent brain slices also identified GABA in the rough ER.

ERAD/Ubiquitination/Seizure Disorders

The exit of $GABA_A$Rs from the ER is negatively regulated by constitutive ER-associated degradation (ERAD) (Gallagher et al., 2007; Saliba et al., 2007; Bradley et al., 2008). ERAD recognition of misfolded proteins leads to their dislocation from the ER membrane, ubiquitination via E3 ligases, and proteosomal degradation in the cytoplasm (Fig. 2). Chronic neuronal blockade via 24 h tetrodotoxin (TTX) treatment increases $\beta3$ subunit $GABA_A$R ubiquitination and ERAD, leading to reduced receptor cell surface expression and decreased inhibition (Saliba et al., 2007). Conversely, enhanced neuronal activity diminished $\beta3$-subunit ubiquitination and improved receptor stability. Reduced calcium entry via voltagegated calcium channels (VGCC) also contributes to ubiquitination and degradation of receptor subunits (Saliba et al., 2009), while enhanced VGCC activity promotes $\beta3$ S383 phosphorylation and receptor insertion (Saliba et al., 2012), suggesting a mechanistic link to activity-dependent changes.

$GABA_A$R subunit mutations that result in enhanced ERAD contribute to genetically determined epilepsies, or idiopathic generalized epilepsies (IGEs) (Fig. 1C). The $\alpha1$ A322D $GABA_A$R subunit mutation causes autosomal dominant juvenile myoclonic epilepsy (Cossette et al., 2002) while the $\gamma2$ R43Q mutation is linked to childhood absence epilepsy. Further studies of familial epilepsy have identified other $\gamma2$ mutants that impair receptor assembly and trafficking (Huang et al., 2014). ER luminal proteins glucose-regulated protein 94 (Grp94) and osteosarcoma amplified 9 (OS-9) recognize and convey misfolded $\alpha1$ subunits to the E3 ligase Hrd1 (*SYVN1* gene) for ubiquitination and ERAD in HEK 293 cells (Fig. 2) (Di et al., 2016). Repression of Grp94 promotes functional surface expression of the misfolded $\alpha1$ A322D mutant subunit, while enhancing proteosomal degradation

machinery reduces WT α1 subunit levels, reinforcing the emerging theme that ERAD is a key regulator of $GABA_AR$ cell surface levels. Changes in $GABA_AR$ ERAD may contribute to other neuronal disorders, as increased levels of Hrd1 and decreased α1 subunit protein levels were observed in middle frontal cortex of autism spectrum disorder (ASD) subjects (Crider et al., 2014). Similarly, the α1 D219N subunit mutant contributing to IGEs is ER retained (Lachance-Touchette et al., 2011). Treatment with the FDA approved drug and L-type Calcium Channel Blocker verapramil enhances recombinant α1D219Nβ2γ2 subunit assembly and ER chaperone calnexin assisted forward trafficking (Han et al., 2015), suggesting proteostasis regulation as a potential therapeutic in treatment of IGEs. An important negative regulator of $GABA_AR$ ERAD is Plic-1 (also known as ubiquilin 1, UBQLN1), a protein with a ubiquitin-like (UBL) proteosomal binding domain and ubiquitin-associated domains. Plic-1 increases stability of $GABA_AR$ in the ER by inhibiting α and β subunit ubiquitination and proteosomal degradation, thereby increasing receptor surface expression (Fig. 2) (Bedford et al., 2001; Saliba et al., 2008).

Forward Trafficking

Once assembled, $GABA_ARs$ undergo transport from the ER to the Golgi apparatus, followed by translocation to the plasma membrane. In the Golgi, the γ2 subunit is subject to palmitoylation by the Golgispecific DHHC zinc finger enzyme (GODZ), a process important for synaptic $GABA_AR$ maintenance and surface expression (Fig. 2) (Keller et al., 2004; Fang et al., 2006). The critical role of this enzyme in palmitoylating the γ2 subunit was validated in GODZ KO mice where loss of this protein resulted in reduced receptor clustering, innervation, and inhibitory strength (Kilpatrick et al., 2016). During Golgi forward transport, $GABA_ARs$ are segregated into distinct vesicles from excitatory glutamatergic AMPA receptors (AMPARs), and are subsequently inserted at the cell surface via specialized RabGTPases and SNARE complexes SNAP23–syntaxin1A/B–VAMP2 and SNAP25–syntaxin1A/B–VAMP2, respectively (Gu et al., 2016). Proteins contributing to $GABA_AR$ trafficking from the Golgi to the plasma membrane include Big2 (brefeldin A-inhibited GDP/GTP exchange factor 2) (Charych et al., 2004), GABARAP (GABA receptor-associated protein) (Wang et al., 1999), GRIP (Glutamate receptor interacting protein) (Charych et al., 2004; Kittler et al., 2004), PRIP1/2 (phospholipase C-related catalyti-cally inactive proteins 1 and 2) (Kanematsu et al., 2002; Uji et al., 2002), $GABA_ARs$-interacting factor (GRIF-1) (Beck et al., 2002), Macoco (Smith et al., 2010), and N-ethylmaleimide-sensitive factor (NSF) (Fig. 2) (Goto et al., 2005). As an Arf guanine exchange factor (GEF), Big2 promotes membrane budding and vesicular trafficking from the Golgi, and can interact with the intracellular loop of all β subunits (Charych et al., 2004). Accordingly, coexpression of Big2 and the β3 subunit increased receptor surface levels in heterologous cells. Big2 has also been identified in recycling endosome membranes (Ishizaki et al., 2008; Boal and Stephens, 2010) and more recent work indicates it contributes to neuronal migration (Zhang et al., 2012, 2013), expanding the neuronal role of this protein. One of the first discovered $GABA_AR$ interacting proteins (Wang et al., 1999), GABARAP is a family member of the UBLs proteins which contain ubiquitin related sequences and control a variety of cellular processes (reviewed in van der Veen and Ploegh, 2012). The UBL GABARAP/GATE-16 subfamily contributes to autophagy and includes GABARAP, GABARAPL1, GATE-16 (Golgi-associated ATPase enhancer of 16 kDa) and GABARAPL3

in mammals (Shaid et al., 2013). Extensively studied (reviewed in Luscher et al., 2011a), GABARAP is concentrated in the Golgi and somatodendritic membrane, interacts with γ subunits and microtubules (Wang et al., 1999), and overexpression increases $GABA_AR$ surface levels (Leil et al., 2004). More recent work revealed GABARAP was essential for NMDA-induced increases in $GABA_AR$ synapses occurring via enhanced exocytosis (Marsden et al., 2007). However, GABARAP is not critical in regulation of surface receptor levels, as GABARAP knockout mice show a normal distribution of γ2-$GABA_ARs$ and gephyrin, suggesting functional redundancy (O'Sullivan et al., 2005). With respect to $GABA_AR$ trafficking and general neuronal autophagic processes, GABARAP/GATE-16 protein family functions remain underexplored.

Multiple GABARAP interacting proteins are implicated in regulation of receptor trafficking or localization including the PDZ domain-containing GRIP, which promotes NMDA dependent $GABA_AR$ synaptic plasticity (Marsden et al., 2007) and glutamatergic AMPAR synaptic stabilization (Dong et al., 1997). A recent study identified missense gain of function mutations in PDZ 4–6 of the GRIP1 gene in autistic patients, resulting in enhanced AMPAR recycling and increased GluA2 surface levels (Mejias et al., 2011). Although $GABA_AR$ dysfunction is heavily implicated in autistic disorders, and GRIP1 binds to gephyrin via PDZ 4–6, $GABA_AR$ synaptic plasticity was not investigated in this study. Both PRIP1/2 and the NSF ATPase interact with $GABA_ARs$ both indirectly via GABARAP and directly with $GABA_AR$ β subunits (Kanematsu et al., 2002; Terunuma et al., 2004; Goto et al., 2005; Mizo-kami et al., 2007). Interestingly, PRIP and γ2 bind to the same site of GABARAP, and PRIP1/2 knockout mice show a reduction in $GABA_AR$ expression and impaired γ2 subunit specific pharmacology including reduced benzodiazepine sensitivity and Zn^{2+} modulation (Kanematsu et al., 2002). NSF is a core component of SNARE-mediated fusion machinery and participates in regulating receptor cell surface trafficking (Chou et al., 2010). NSF also interacts with AMPAR, playing an essential role in receptor insertion, synaptic stabilization and endosomal recycling (reviewed in Anggono and Huganir, 2012), suggesting overlapping regulation of excitatory and inhibitory receptor trafficking.

Vesicular $GABA_AR$ transport from the trans-Golgi network to the plasma membrane relies on the microtubule-dependent molecular motor kinesin KIF5 family (KIF5A, KIF5B, KIF5C) (Fig. 2) (Twel-vetrees et al., 2010). KIF5A binds to GABARAP *in vivo* (KIF5B and KIF5C do not bind GABARAP), and contributes to $GABA_AR$ trafficking to the neuronal surface (Nakajima et al., 2012). Conditional knockout of KIF5A in mice results in deficits of $GABA_AR$ plasma membrane levels, seizures, and 75% lethality within 3 weeks (Nakajima et al., 2012). In addition to forward trafficking, KIF5 contributes to post-endocytic receptor transport via HAP1 (hun-tingtin-associated protein 1) (to be described further in the recycling section). FGF7 (fibroblast growth factor 7) is an inhibitory postsynaptic cell derived organizer of GABAergic presynaptic terminals (Ter-auchi et al., 2010) that requires gephyrin and KIF5-dependent transit for synapse targeting (Fig. 2). An additional kinesin family protein, KIF21B, was recently demonstrated to co-precipitate with the $GABA_AR$ γ2-subunit and colocalize at GABAergic synapses in neurons (Labonte et al., 2014). Knockdown of KIF21B by shRNA methods decreased receptor surface levels and the intensity of extrasynaptic γ2 clusters, but did not affect synaptic $GABA_ARs$ concentration opposed to presynaptic terminals labeled with synaptic vesicle glycoprotein 2A.

Scaffolding proteins such as gephyrin are often used as adaptor proteins for transporting receptors to synapses (Kneussel, 2005). FGF7 and gephyrin traffic together via KIF5, strongly suggesting that many inhibitory synapse components including $GABA_AR$, gephyrin, GABARAP and FGF7 may travel together in a complex. Another KIF5 interactor, GRIF-1/traf-ficking kinesin binding protein 2 (TRAK2) (Brickley et al., 2005), also associates with the $GABA_AR$ $\beta 2$ subunit (Beck et al., 2002), although identification of direct interaction with receptors in the brain is lacking and the role of TRAK family kinesin adaptors in $GABA_AR$ trafficking remains unclear (reviewed in Stephenson, 2014). Finally, Maf1 and the Maf1interacting protein Macoco were shown to interact with $\beta 3$ subunits via yeast two-hybrid assays, with Macoco overexpression increasing receptor surface expression (Fig. 2) (Smith et al., 2010). Although Maf1 was originally identified in yeast as a repressor of transcription (Pluta et al., 2001; Upadhya et al., 2002), further insight into Maf1 neuronal function has not occurred.

A recent interest has emerged in understanding the role of disrupted in schizophrenia (DISC1) protein in $GABA_AR$ trafficking, as genomic screenings have linked mutations of DISC1 to psychiatric illnesses (Devine et al., 2016). Overexpression of wild-type DISC1 leads to enhanced $GABA_AR$ surface expression and miniature inhibitory postsynaptic currents (mIPSCs) in a KIF5-dependent manner, while knockdown of this protein has the opposite effect (Fig. 2) (Wei et al., 2015). Furthermore, Saito et al. (2016) found postnatal knockdown of DISC1 in mouse prefrontal cortex disturbs dendritic development, reduces $\alpha 2$-containing $GABA_AR$ synaptic clustering, decreases mIPSC amplitude, and causes sensorimotor defects (Saito et al., 2016). This work also provided evidence that DISC1 specifically regulates $\alpha 2$-containing $GABA_ARs$ in immature neurons, and pharmacological agents enhancing $\alpha 2/\alpha 3$-containing $GABA_AR$ channel function could reverse the behavioral defects seen in DISC1 mutant mice. Studies using DISC1 total knockout mice demonstrate a loss of GABAergic interneurons within the prefrontal cortex and loss of total cell density in the deep layers of the cortex (Umeda et al., 2016), as well as a reduction in neuropeptide-Y expressing neurons and their respective fiber length (Morosawa et al., 2017). Interestingly, GABA-induced NKCC1-dependent depolarization is critical for regulation of dendritic development during adult hippocampal neurogenesis via AKT-mTOR signaling (Kim et al., 2012). Moreover, human patients with schizophrenia exhibited a significant interaction between single nucleotide polymorphisms in DISC1 and the chloride-regulator NKCC1 (SLC12A2). These findings were later confirmed using functional MRI studies in two human subjects who were homozygous for both these risk alleles, identifying that hippocampal connectivity and responsiveness were diminished in a recognition memory task (Callicott et al., 2013). The evolving story of DISC1's role in $GABA_AR$ trafficking and function in development and cognitive impairment represents an exciting area of research into the basis of certain psychiatric illnesses.

THE GABAERGIC SYNAPSE

Gephyrin

The confinement of $GABA_ARs$ at synaptic sites is a key step in tuning the strength of phasic inhibition. The post-synaptic inhibitory scaffolding protein gephyrin is the main organizer of

$GABA_AR$ synaptic localization and density (Jacob et al., 2005), as gephyrin knock out mice exhibit a robust loss of $GABA_AR$ clustering (Kneussel et al., 1999), although gephyrin-independent synaptic clustering does occur (Kneussel et al., 2001; Levi et al., 2004). Gephyrin is a highly conserved 93 kDa protein that is hypothesized to form multimeric complexes which associate with a number of cytoskeletal proteins (Giesemann et al., 2003), contributing to its scaffolding function (Tretter et al., 2012). The architecture of gephyrin scaffolding arises from the N terminal or G domain of gephyrin participating in dimer-dimer self-associations, while the C terminal or E domain forms trimer interactions, likely to create a hexagonal lattice (Fig. 3) (Kneussel and Betz, 2000; Saiyed et al., 2007). This structure tethers freely-diffusing receptors at synaptic sites through binding $GABA_AR$ a1, α2, α3, α5, β2, and β3 subunits (Tretter et al., 2008; Wu et al., 2012; Kowalczyk et al., 2013; Brady and Jacob, 2015). The $GABA_AR$ γ2 subunit also plays an important role in gephyrin-receptor attachment, as γ2-knockout mice demonstrate diminished clustering of gephyrin and $GABA_ARs$ (Gunther et al., 1995; Essrich et al., 1998). Importantly, synaptic $GABA_AR$ clustering can occur independent of y2 in some cases (Kerti-Szigeti et al., 2014). Functionally, gephyrin acts to confine receptors undergoing diffusion at the cell surface membrane and limit their escape into the extrasynaptic space, a process that is influenced by neuronal activity (see section on activity-dependent plasticity of $GABA_AR$ synapses) and $GABA_AR$ specific drugs including the benzodiazepine, diazepam (Gouzer et al., 2014; Levi et al., 2015). Gephyrin's scaffolding ability is influenced by extensive posttranslational modifications (Fig. 5). Mass spectrome try studies alone have revealed 22 sites of phosphory lation in gephyrin's C domain and 1 additional threonine 324 site in the E-domain (Herweg and Schwarz, 2012; Kuhse et al., 2012; Tyagarajan et al., 2013). Yet, the exact role of gephyrin phosphoryla tion is complex and controversial, highlighted by the bidirectional effect of altering gephyrin phosphoryla tion at the serine (S) 270 site. Initial findings by Tyagarajan et al. (2011) identified phosphorylation of this site by Glycogen Synthase Kinase 3β to nega tively modulate gephyrin clustering, possibly due to enhanced Ca^{2+}-dependent protease calpain−1 mediated degradation. Accordingly, overexpression of a phosphodeficient S270A gephyrin mutant enhanced both the amplitude and frequency of mIPSCs, sugges ting increased functional $GABA_AR$ clustering. It was later revealed that the S270 site was also a substrate for the proline-directed serine/threonine kinase, cyclin-dependent kinase 5 (CDK5) (Kuhse et al., 2012; Kalbouneh et al., 2014). Gephyrin synaptic clusters were found to be basally phosphorylated at Ser270 in a CDK5-dependent manner (Kuhse et al., 2012), with CDK5 knockdown or inhibition leading to loss of phosphorylated gephyrin clusters and postsynaptic γ2-containing $GABA_ARs$ (Kalbouneh et al., 2014). To further complicate these findings, S270 is cross-regulated by phosphorylation of a neighboring S268 residue targeted by extracellular signalregulated kinase 1/2 (Tyagarajan et al., 2013) (role for ERK also described in Wuchter et al., 2012). This study suggested these serine residues control distinct gephyrin clustering dynamics including postsynaptic cluster size and number, again in conjunction with calpain activity. Expanding the role of gephyrin serine site regulation, phosphomutant studies and *in vitro* kinase assays indicate that increased phosphory lation of gephyrin on S305 (phosphopeptide mass spectrometry identification Tyagarajan et al., 2013) by the kinase CAMKII is required for activitydependent inhibitory plasticity (Flores et al., 2015). Considering the number of additional gephyrin phos phorylation sites identified *in vivo* and the challenges of gephyrin

point mutant studies (overexpression concerns), continued multidisciplinary efforts are necessary to resolve the functional relevance of these modifications.

Other post-translational modifications including SUMOylation, acetylation, and palmitoylation are important regulators of gephyrin function. Gephyrin G- and E-domain lysine (K) residues can undergo SUMOylation and acetylation *in vitro* and *in vivo* (Ghosh et al., 2016). Ghosh et al. (2016) found conju gation of the small UBL modifier (SUMO)1 or SUMO2 to the K148 or K724 site, respectively. Overexpression of gephyrin with lysine-to-arginine mutations at these sites reduces gephyrin scaffolding and postsynaptic $GABA_AR$ strength as evidenced by reduced mIPSC in cultured neurons. Accordingly, gephyrin SUMOylation and clustering is regulated by the E3 SUMO-ligase protein inhibitor of activated STAT3 (PIAS3). PIAS3 modulation of gephyrin organization is negatively influenced by acetylation of gephyrin at a K666 site. Collectively, this work provides evidence of functional crosstalk between gephyrin phosphorylation, acetylation, and SUMOy-lation to dictate formation of postsynaptic clustering and to conversely dynamically alter gephyrin cluster size and density. Palmitoylation of gephyrin cysteine residues by the palmitoyl acyltransferse DHHC-12 also appears essential for gephyrin synaptic cluster ing, an enzymatic-process fine-tuned by changes in GABAergic activity (Dejanovic et al., 2014). Gephyrin further interacts with neuronal nitric oxide synthase and is subject to S-nitrosylation, a modifica tion that reduces gephyrin cluster size, while pharma cological inhibition of nitric oxide reverses this process and increases the number of cell surface syn aptic $GABA_ARs$ (Dejanovic and Schwarz, 2014). How these collective post-translational modifications act in concert to regulate gephyrin scaffolding and clustering properties remains poorly understood.

A major contributor to gephyrin accumulation and stability at GABAergic synapses is the Dbl-like GEF, collybistin (Fig. 3). Collybistin is a RhoGEF expressed in three major isoforms (1–3) that functions as an important intermediary for gephyrin traf ficking to synapses (Harvey et al., 2004). Collybistin's scaffolding role results from its direct interaction with the gephyrin E domain, the plasma membrane via a pleckstrin homology domain, and a Src-homology-domain—3 (SH3) in specific isoforms. The SH3 domain enzymatically activates the small GTPase CDC42, a known regulator of actin dynam ics. CDC42 directly interacts with the presynaptic scaffolding protein NL2 to facilitate gephyrin synap tic accumulation (Poulopoulos et al., 2009; Soykan et al., 2014) (see trans-synaptic components of GABAergic synapses section), a process negatively regulated by phosphorylation of NL2 by the prolinedirected kinase Pin1 (Antonelli et al., 2014). The SH3-domain further forms a direct contact with the $GABA_AR$ $\alpha 2$ subunit to strengthen gephyrin binding interactions, while the $\alpha 3$ subunit binds gephyrin independent of collybistin (Saiepour et al., 2010; Tretter et al., 2011), suggesting a cell or synapse specific role of collybistin in regulating gephyrin cluster ing and $GABA_AR$ scaffolding function. In support of this argument, collybistin knock-out mice demon strate selective loss of gephyrin and $GABA_AR$ clus tering in braiand compartment-specific regions, culminating in reduced GABAergic neurotransmis sion, anxiety, and impaired spatial learning (Papadopoulos et al., 2007). Alterations in cellular levels of phosphatidylinositol 3-phosphate have also been demonstrated to critically regulate gephyrin synaptic accumulation and GABAergic neurotransmission, likely via collybistin (Papadopoulos et al., 2017).

Less investigated means of gephyrin regulation have also emerged. The axon growth regulating pro tein growth-associated protein 43 (GAP43) was recently found to play an important role in gephyrin aggregation state and $GABA_AR$ clustering in devel oping neurons (Wang et al., 2015). GAP43-association with gephyrin is enhanced during conditions of reduced PKC and neuronal activity in devel oping cortical neurons, resulting in gephyrin misfolding. RNA level regulation of gephyrin scaf folding function by the non-octamer-containing, POU-domain DNA-binding protein (NONO), is implicated in certain patients with intellectual dis ability (Mircsof et al., 2015). NONO participates in neuronal RNA transport complexes (Kanai et al., 2004), its concentration at synapses is activity-dependent (Zhang et al., 2012), and one-third of its target transcripts are synaptic proteins (Mircsof et al., 2015). NONO-deficient mice demonstrate gross aber rations in dendrite morphology, gephyrin scaffolding, reductions in $GABA_AR$ α2-subunit levels, and pheno typic and behavioral changes suggesting syndromic intellectual disability (Mircsof et al., 2015).

Diverse $GABA_AR$ subtype- and region-specific synapse constituents highlight the complexity of GABAergic neurotransmission. For example, the cell adhesion molecule (CAM) neuroplastin-65 (Fig. 3), which is prominently expressed during synaptogenesis (Watson et al., 2006), is localized at α1 and α2-subunit containing $GABA_AR$ synapses, but not α3 (Sarto-Jackson et al., 2012) (much like collybistin). shRNA knockdown of neuroplastin-65 reduces α2 synaptic levels *in vitro,* while *in vivo* knockout models demonstrate an enhanced $\alpha1/\alpha2$ subunit ratio at GABAergic synapses without a change in gephyrin levels opposed to presynaptic terminals positive for the vesicular inhibitory amino acid transporter (VIAAT), suggesting neuroplastin-65 has a selective regulatory role in α2 $GABA_AR$ accumulation (Sarto-Jackson et al., 2012; Herrera-Molina et al., 2014). The CAM neurofascin facilitates developmental clus tering of gephyrin on the axon hillock and is critical for axo-axonic GABAergic synapse clustering (Bur-karth et al., 2007; Kriebel et al., 2011). Accordingly, knockdown of neurofascin in the basolateral amyg dala of mice results in reduced GABAergic input at the axon initial segment (AIS), impaired synaptic plasticity and excitability, and hindered fear extinc tion in behavioral testing (Saha et al., 2017). It is important to note that most $GABA_AR$ clusters along the AIS contain a α2 subunit (Nusser et al., 1996; Brunig et al., 2002; Muir and Kittler, 2014; Gao and Heldt, 2016). Interestingly, *in vivo* viral expression of a chimera construct containing the TM3-TM4 region of a1 and the α2 intracellular gephyrin binding loop selectively disrupts α2-$GABA_AR$ clustering periso-matically, but not at the AIS in the frontal cortex of mice (Hines et al., 2013). Expression of this domi nant negative chimera, by interfering with endoge nous α2 and gephyrin interaction, led to the replacement of somatic clusters of α2 with α1, reduced γ-power, and working memory deficits in mice. These findings illuminate an interesting ques tion about the differences in composition of inhibi tory synapses at the AIS versus the soma and why interference with α2-gephyrin binding has divergent effects. The unique nature of axo-axonic synaptic plasticity is highlighted by optogenetic excitation studies in hippocampal neurons demonstrating physi cal relocation of the AIS but not repositioning of axo axonic GABAergic synapses (Wefelmeyer et al., 2015).

Trans-Synaptic Components of GABAergic Synapses

One of the most well characterized trans-synaptic interactions crucial for $GABA_AR$ synapse develop ment is that of neuroligins and neurexins (Fig. 3) (Varoqueaux et al., 2006). Neurexins are found presynaptically and induce differentiation of GABAergic and glutamatergic post-synaptic densi ties during maturation and plasticity (Graf et al., 2004; Krueger et al., 2012), although overexpression of neurexins leads to reduced GABAergic neurotrans mission (Zhang et al., 2010). The calsyntenins are another adhesion family governing synapse forma tion, with calsyntenin-3 identified as an a-neurexin interactor (Pettem et al., 2013; Lu et al., 2014) that contributes to inhibitory synapse development and neurotransmission (Pettem et al., 2013; Um et al., 2014). Dystroglycan (DG), a core component of the dystrophin-glycoprotein complex, is an additional α- neurexin interactor that regulates $GABA_AR$ synaptic scaffolding and plasticity (Levi et al., 2002; Graf et al., 2004; Pribiag et al., 2014). Studies using conditional deletion of Dag1 (DG) in pyramidal cells show diminished innervation of CCK-positive interneurons while parvalbumin positive basket cell terminals are unaffected, indicating a cell-type and synapse-specific trans-synaptic function (Friih et al., 2016; Panzanelli et al., 2017). Postsynaptically, different neuroligins (NL1–4) are found at either glutamatergic or GABAergic synapses and play important scaffold ing and receptor recruitment roles. GABAergic syn apses primarily rely on NL2 for synapse integrity, and when expressed with recombinant $GABA_ARs$ in HEK cells, NL2 supports formation of functional GABAergic synapses in neuron co-culture systems (Dong et al., 2007). Moreover, NL2 is critical for GABAergic synapse formation and coding in the ret ina (Hoon et al., 2009), while enhanced expression of this protein in cerebellar granule cells can accelerate $GABA_AR$ synapse development (Fu and Vicini, 2009; Brown et al., 2014) and strengthen inhibitory synaptic function in hippocampal neurons (Chubykin et al., 2007). Despite these observations, functional $GABA_AR$ synapses can also form in HEK-neuron co culture systems independent of NL2 (Fuchs et al., 2013), a process dependent on the N-terminal ECDs of $GABA_AR$ subunits (Brown et al., 2016). Intrigu ingly, NL1–3 triple knockout mice suggest loss of these proteins does not alter the total number of syn apses occurring in hippocampal, neocortical, or brainstem neurons, but results in a profound reduc tion in spontaneous IPSC and a minor decrease in glutamatergic activity in brainstem slices, ultimately resulting in an enhanced excitatory/inhibitory ratio and respiratory failure (Varoqueaux et al., 2006). The number of asymmetric and symmetric synapses is unchanged in the hippocampus of NL2 lacking mice as measured by electron microscopy, yet VIAAT pos itive puncta and IPSC amplitude are reduced and an anxiety phenotype is seen (Chubykin et al., 2007;Blundell et al., 2009). The anxiety phenotype in NL2 KO mice has been suggested to result from reduced perisomatic inhibitory synapses in the basal amyg dala and hyperactivity of projection neurons in this region (Babaev et al., 2016). Furthermore, selective knockout of NL2 in the medial prefrontal cortex of mice has been shown to reduce synaptic inhibition after 6–7 weeks and produce cognitive impairment phenotypes (Liang et al., 2015).

The recent discovery of the NL2 interacting GARLH family proteins proposed to function as $GABA_AR$ auxiliary subunits, more specifically lipoma HMGIC fusion partner-like 3 and 4 (LH3 and LH4), further advances our knowledge of $GABA_AR$ clustering and regulation (Fig. 3) (Yamasaki et al., 2017). Auxiliary subunits previously described for other ligand-

gated ion channels, including AMPA and kainate glutamate receptors, influence channel characteristics or receptor localization (Jackson and Nicoll, 2011; Yan and Tomita, 2012). Yamasaki et al. (2017) demonstrated native $GABA_AR$ com plexes contain LH4 in the cerebellum and hippocam pus, with this protein likely acting as a bridge between synaptic $GABA_AR$ γ2-subunits and NL2 to provide synaptic anchoring properties. Accordingly, knockdown of LH4 *in vitro* and *in vivo* results in a dramatic reduction of γ2-synaptic clustering and inhibitory neurotransmission (Yamasaki et al., 2017). The evolutionarily conserved extracellular synaptic organizing protein, MADD-4/Ce-punctin, also is a recently discovered neuroligin binding partner and a critical mediator of GABAergic synapse formation in *Caenorhabditis elegans (C. elegans)* (Maro et al., 2015; Tu et al., 2015). The evolving knowledge of newly identified and additional unknown GABAergic trans-synaptic proteins may prove highly insightful to human health conditions and disorders.

$GABA_AR$ stability at synapses is also influenced by actin cytoskeletal interactions occurring between gephyrin and the microfilament system (Giesemann et al., 2003; Bausen et al., 2006). Recent work identified $GABA_AR$ direct regulation via an actinremodeling pathway originating at the signaling scaf fold protein G protein-coupled receptor kinaseinteracting protein 1 (GIT1) and the GEF βPix (Fig. 3) (Smith et al., 2014). GIT1 and βPix form native complexes with $GABA_AR$ subunits, and mediate downstream activity of the Rho family GTPase Rac1 and the effector p21-activating kinase to pro mote receptor synaptic stability. Our current overall understanding of the proteins involved in inhibitory synapse stability and clustering remains incomplete, as highlighted by two recent *in vivo* inhibitory synapse proteomic screenings using α2-pHluorin (pH-sensitive GFP) tagged subunit knock-in mice (Nakamura et al., 20l6) or viral expression of inhibi tory fusion proteins including gephyrin (Uezu et al., 20l6). These mass spectrometry methods revealed l40 (Uezu et al., 20l6) and l49 (Nakamura et al., 20l6) novel protein components of $GABA_AR$/inhibitory synapses spanning multiple trafficking, stability, and regulatory pathways. Collectively, these studies further validated molecular interactions between $GABA_AR$ intracellular loops and the metabotropic glutamate receptor subunit mGluR5, the Dbl family GEF Ephexin, the metabotropic GABA B receptor ($GABA_BR$) auxiliary subunit KCTDl2, and initiated characterization of a novel inhibitory synaptic regula tor inhibitory synaptic protein l (InSynl). Future investigations will need to dissect the exact roles of these identified proteins in $GABA_AR$ regulation and function.

Extrasynaptic $GABA_ARs$

Although synaptic receptors participate in phasic inhibition, extrasynaptic $GABA_ARs$ are responsible for setting the inhibitory tone of a neuron through the generation of a constant tonic current. Receptors composed of $\alpha4\beta\delta$ or $\alpha6\beta\delta$ subunits are found extrasynaptically and respond to low concentrations of ambient or “spillover” GABA (Fig. 3) (Saxena and Macdonald, l996; Haas and Macdonald, l999; Ke et al., 2000; Bianchi et al., 200l; Brown et al., 2002; Terpstra et al., 2002). Although hippocampal tonic currents are largely generated by synaptic spillover (Glykys and Mody, 2007b), other GABA sources include astrocytes (Liu et al., 2000; Kozlov et al., 2006), and neurogliaform cells (Olah et al., 2009). Furthermore, extrasynaptic $GABA_ARs$ can be sponta neously open in the absence of GABA (Wlodarczyk et al., 20l3). $GABA_ARs$ incorporating the α5-subunit with $\beta\gamma$2 also represent a

large pool of extrasynaptic GABAergic signaling (Brunig et al., 2002; Crestani et al., 2002), although this receptor subtype can be found clustered both synaptically (Serwanski et al., 2006; Zarnowska et al., 2009; Brady and Jacob, 20l5) and extrasynaptically (Loebrich et al., 2006). Scaffolding of $\alpha5\beta\gamma2$ $GABA_A$Rs extrasynaptically occurs due to interaction with the ERM family pro tein radixin (Fig. 3) (Loebrich et al., 2006), whereas $\alpha5$ was recently shown to interact with gephyrin at synaptic sites (Brady and Jacob, 20l5). Radixin acts in a phospho-dependent manner to scaffold $\alpha5\beta\gamma2$ receptors to the actin cytoskeleton ultimately reducing diffusion rates and concentrating channel activity away from axon terminals (Hausrat et al., 20l5). Bidirectional control of radixin phosphorylation state by the RhoA GTP- and Rho-kinase (ROCK) dependent pathway is contingent on GABAergic versus glutamatergic activity (Fig. 3). Application of GABA favors radixin phosphorylation and retention of $\alpha5$-$GABA_A$Rs extrasynaptically, while AMPA treatment leads to dephosphorylation and increased percentage of $\alpha5$-subunit receptors found synaptically (Hausrat et al., 20l5). Additional $GABA_A$R subtypes are also subject to synaptic/extrasynaptic exchange following manipulations of the excitatory/inhibitory balance and/or kinase signaling. Gerrow and Triller (20l4) identified $GABA_B$R activity increases $\alpha2$-$GABA_A$Rs diffusion from synapses via PKC activity, allowing $\alpha5$-$GABA_A$R synaptic accumulation due to available synaptic binding slots (Gerrow and Triller, 20l4). PKC-activation also promotes synaptic accumulation of $\alpha4$-containing $GABA_A$Rs (Carlson et al., 20l6), while PKA-activation shifts $\alpha4$-receptors extrasynap tically (Fig. 3) (Carlson et al., 20l6). These findings highlight the dynamic nature of $GABA_A$R synaptic/extrasynaptic exchange and the diverse mechanisms to fine-tune GABAergic neurotransmission.

$GABA_A$R INTERNALIZATION, RECYCLING, AND LYSOSOMAL DEGRADATION

$GABA_A$R Internalization

Regulated internalization of cell surface receptors is a universal cellular response to moderate signaling and function. $GABA_A$R internalization occurs through clathrin-mediated endocytosis dependent on dynamin (the GTPase that is responsible for fission of endocytic vesicles from the plasma membrane) and binding of the adaptor protein AP2 to specific $GABA_A$R subunits (Fig. 4) (Kittler et al., 2000), although clathrin-independent endocytosis occurs in heterologous cells and in *C. elegans* (Cinar and Barnes, 200l; Rowland et al., 2006). The interaction of AP2 with $GABA_A$Rs is partly regulated by PKA and PKC mediated-phosphorylation of serine residues within a highly basic ten amino acid sequence motif in the intracellular loop of the β subunits (S409 in $\beta1$, S4l0 in $\beta2$, S408/409 in $\beta3$), with increased phosphorylation reducing AP2 and $GABA_A$R interaction and endocytosis (Fig. 4) (McDonald et al., l998; Brandon et al., 2002, 2003; Kittler et al., 2005; Smith et al., 2008). Two additional motifs in the β-subunit appear important for AP2 interactions: (l) a dileucine motif is critical for receptor internalization in HEK cells (Herring et al., 2005) and (2) three argi nine residues (405RRR407) within the $\beta3$-subunit intracellular domain are important for AP2-stabilization of receptors at dendritic endocytic zones (Smith et al., 2012). Accordingly, benzodiazepine resistance in epileptic mice undergoing sustained seizures is linked to reductions in PKC phosphoryla tion of β subunits and loss of surface receptors (including benzodiazepine-sensitive $\gamma2$ $GABA_A$Rs) (Terunuma et al., 2008).

Moreover, S408/409D phosphomimetic mutants were recently shown to block oxygen-glucose deprivation (OGD) induced receptor internalization and reduce cell death in cultured hip pocampal neurons (Mele et al., 2014). The impor tance of phosphoregulation of these residues was revealed by S408/409A homozygous mice (the S/A mutation reduces AP2 interaction, mimicking phos phorylation; Jacob et al., 2009), which exhibit increased phasic but decreased tonic inhibition, and demonstrate the core phenotypes of ASDs (Vien et al., 2015). Moreover, a common model of fragile X syndrome and ASDs, the Fmr1 KO mouse, demon strates enhanced S408/409 phosphorylation, further providing evidence for deregulation of these sites in disease (Vien et al., 2015). How specific PKC isoforms participate in phosphoregulation of $GABA_AR$ surface levels and internalization is still unclear. For instance, ethanol induced internalization of α1-containing $GABA_ARs$ is PKCγ dependent (Kumar et al., 2010), while PKCε reduces $GABA_AR$ sensitivity to ethanol and BZs by acting at a γ2 S327 residue (Qi et al., 2007).

The intracellular loop of the γ2 subunit also con tains two AP2 interactions domains, a 12 basic amino acid region similar to the β-subunits and a classical YGYECL motif (Smith et al., 2008). The Tyr 365/367 within the YGYECL motif are targets of Fyn and other Src family kinases (Fig. 4) (Brandon et al., 2001; Jurd et al., 2010), and phosphorylation at these sites reduce AP2 binding (Kittler et al., 2008). Tyro sine to phenylalanine mutations inhibits AP2 binding to the γ2 subunit, and heterozygous Y365/7F knock-in mice demonstrate surface and synaptic accumula tion of $GABA_ARs$ and spatial memory deficits (Tret-ter et al., 2009). Importantly, homozygous Y365/7F knock-in mice are developmentally lethal, highlight ing the importance of these residues in regulating $GABA_AR$ activity. BDNF-induced phosphorylation of the γ2 subunit Y365/7 residues was recently impli cated as a promoter of receptor surface expression during hippocampal neurogenesis (Vithlani et al., 2013). The authors found heterozygous Y365/7F mice demonstrated an antidepressant-like phenotype and enhanced neurogenesis that could not be further enhanced by BDNF. Interestingly, Y365/7F mice also exhibit sex-specific alterations in both dentate gyrus granule cells (Kretschmannova et al., 2013) and thalamic relay neurons of the dorsal lateral genic ulate nucleus (Nani et al., 2013), where female mice have increased α4 and δ subunit levels and associated increased tonic inhibition, changes not seen in male mice. Alpha subunit composition may also play a role in regulating endocytosis, as heterozygous α1 subunit deletion mice, which develop absence epi lepsy, exhibit reduced clathrin-mediated endocytosis of α1-containing $GABA_ARs$ and an increase in the relative fraction of residual a1 at the cell surface (Zhou et al., 2013). Neurons from these mice have reduced mIPSCs, altered current kinetics and respon siveness to BZs, possibly due to changes in receptor α1/α3 ratios and β2 subunit proportions. Giant ankryin-G, a protein typically characterized to be important for AIS assembly and scaffolding (Bennett and Lorenzo, 2013), was recently found to be a novel regulator of somatodendritic $GABA_AR$ synaptic sta bilization (Fig. 4) (Tseng et al., 2015). Mitigation of $GABA_AR$ internalization by giant ankryin-G was found to be dependent on interaction with GABARAP via a neuronal specific exon-coding sequence at extrasynaptic sites, with knockdown of giant ankyrin-G leading to enhanced $GABA_AR$ endocytosis, while overexpression reduced it.

With respect to extrasynaptic receptors, the intracellular domain of the δ subunit also binds to the μ2 subunit of AP2 (Fig. 4) (Kittler et al., 2005). Mutation of two AP2 interacting

motifs, a YxxΦ motif and an atypical R/K-rich motif, abolish association of GST-δ-intracellular domain fusion protein with the μ2 subunit of AP2 by pull-down assay (Gonzalez et al., 2012). Interestingly, 5–10 min ethanol expo sure enhances β subunit S408/409 phosphorylation, while simultaneously increasing association of the AP2 μ2-subunit with δ-containing $GABA_A$Rs, sug gesting receptor composition dependent AP2 recruit ment, consistent with rapid ethanol induced impairment in α4βδ $GABA_A$Rs seen *in vivo* and in cultured neurons (Gonzalez et al., 2012). Chronic exposure to the benzodiazepine site antagonist fluma-zenil, recently identified as a negative modulator at α4βδ $GABA_A$Rs, also enhances endocytosis and deg radation of α4βδ recombinant receptors via a clathrin-dependent pathway in heterologous cells (Kuver and Smith, 2016).

A number of noxious stimuli trigger $GABA_A$R endocytosis including seizure models (Goodkin et al., 2005, 2008; Naylor et al., 2005), OGD conditions (Arancibia-Carcamo et al., 2009), and prolonged ago nist application (Chaumont et al., 2013). Protein phosphatases (Fig. 4) have an important role in regu lating receptor endocytosis under these conditions. For example, inhibition of the calcium-sensitive phosphatase calcineurin (CaN) by FK506 or serine/threonine protein phosphatase 1 (PP1) and 2A (PP2A) by okadaic acid reverses reduction of surface γ2-subunit containing $GABA_A$Rs and mIPSC ampli tude induced by status epilepticus treatments in slice preparations (Joshi et al., 2015). NMDA receptor mediated calcium entry and CaN activation was further shown to decrease surface α2-containing recep tors during *in vitro* epileptiform activity by live-cell imaging techniques (Eckel et al., 2015). Activation of the transient receptor potential cation channel sub family V member 1 also appears to cause $GABA_A$R endocytosis in the dentate gyrus of rodents dependent on calcium influx, CaN, and dynamin-activity (Cha vez et al., 2014). In addition, inflammation and release of the proinflammatory cytokine tumor necro sis factor-α (TNFα) stimulates $GABA_A$R internaliza tion (α1/2/5, β3, γ2) in a CaN-independent pathway in cultured hippocampal neurons (Pribiag and Stellwagen, 2013). Activation of TNF receptor 1 by TNFα initiates a p38 MAPK/PI3K/PP1 and dynamin GTPase pathway prompting dephosphorylation of S408/409 on the β3 subunit, reduction of mIPSC amplitude, and diminished gephyrin synaptic clustering. Conversely, activation of p38 MAPK by the cytokine interleukin−1β increases surface expression of the α5-subunit, augmenting tonic current and reducing excitatory long-term potentiation, a process involved in inflammation-induced memory deficits in the hippocampus (Wang et al., 2012). Moreover, this work found TNFα exposure did not significantly alter tonic current. These opposing findings suggest non-p38 MAPK downstream effectors activated by TNFα and interleukin−1β, respectively, may influence activity and recruitment of proteins like PP1. Recent evi dence has also recognized the amyloid β (Aβ) peptide, most commonly associated with the patho genesis of Alzhimer's disease, as a stimulator of $GABA_A$R endocytosis (Ulrich, 2015). Acute applica tion of the Aβ 1–42 peptide fragment decreased GABAergic current in somatosensory cortical slices and this effect was reversed by inhibiting dynamin. The specificity of $GABA_A$R subtypes undergoing Aβ treatment induced internalization remains to be identified.

$GABA_AR$ Recycling

Surface biotinylation assays suggest the majority of constitutively internalized $GABA_ARs$ rapidly recycle back to the cell surface (70% in 1 h), while significant degradation occurs over longer time scales (6 h) (Kittler et al., 2004). The recycling of $GABA_ARs$ is partly mediated by HAP1 direct association with the β subunits (Fig. 4) (Kittler et al., 2004; Twelvetrees et al., 2010). HAP1 functions as a kinesin adaptor and localizes to early endosomes containing $GABA_AR$, and thus overexpression of HAP1 pro motes receptor surface levels and reverses intracellu lar accumulation of receptors by constitutive (Kittler et al., 2004) and OGD-induced endocytosis (Mele et al., 2017). Mutation of the HAP1 protein resulting in polyglutamine expansion, as seen in Huntington's Disease, results in dysregulated transport of $GABA_ARs$ to the cell surface and compromised inhibitory neurotransmission (Twelvetrees et al., 2010). Moreover, Huntingtin protein and HAP1 have recently been identified as a key regulator of autopha gosome transport in neurons (Wong and Holzbaur, 2014). The recycling activity of HAP1 likely arises from its association with the kinesin KIF5 (Fig. 4). Purified complexes of β3-$GABA_AR$/KIF5 and HAP− 1/KIF5 are readily immunoprecipitated from rat brain tissue, while acute blockade of KIF5 reduces $GABA_AR$ synaptic levels and signaling strength (Twelvetrees et al., 2010). The integral membrane protein CAML (calcium-modulating cyclophilin ligand) has also been implicated in $GABA_AR$ for ward trafficking and recycling via interaction with the γ2 subunit cytoplasmic and fourth transmembrane domain regions (Yuan et al., 2008). CAML-deficient neurons have reduced recycling of internalized $GABA_ARs$ and decreased GABAergic neurotrans mission in electrophysiological recordings.

Lysosomal Degradation

$GABA_ARs$ undergoing constitutive internalization from the cell surface may be subjected to lysosomalmediated degradation (Fig. 4), a process blocked by the lysosomal proteolytic inhibitor leupeptin (Kittler et al., 2004). Acute leupeptin treatment also increases the size, number, and strength of GABAergic synap ses in cortical slices (Arancibia-Carcamo et al., 2009). Certain stimuli can also accelerate degradation of surface $GABA_ARs$. For instance, cultured hippo campal neurons undergo enhanced lysosomalmediated degradation of α2-containing receptors in response to benzodiazepine treatment (Jacob et al., 2012). Ubiquitination of 7 lysine residues within the intracellular loop of the γ2 subunit plays a key role in $GABA_AR$ lysosomal targeting (Arancibia-Carcamo et al., 2009). Mutation of these lysines to arginine (K7R) reduced colocalization of receptors at late endosomes, made receptors impervious to leupeptin treatment in heterologous cells, and blocked an OGD-induced loss of surface receptor clusters (Ara-ncibia-Carcamo et al., 2009). The ubiquitin E3-ligase, ring finger protein 34 (RNF34), directly inter acts with the intracellular loop of γ2, co-immunoprecipitates with this subunit from brain extracts, and can be found colocalized at GABAergic synapses (Fig. 4) (Jin et al., 2014). Overexpression of RNF34 enhances the rate of γ2-$GABA_AR$ degrada tion and reduces $GABA_AR$ synaptic cluster size and strength. Interestingly, expression of the γ2 K7R mutant in these experiments did not reverse RNF34-induced degradation of $GABA_ARs$ in co-transfected HEK293 cells, but mutation of additional lysine resi dues in a K8R, K9R, and K10R mutant did. More over, RNF34 mediated ubiquitination appears to contribute to both proteasomal and lysosomal degra dation of $GABA_ARs$ in these cells. The ARF GEF, Brefeldin A-inhibited guanine

nucleotide-exchange protein 3 (BIG3), may also be important for lyso somal trafficking of $GABA_A$Rs (Fig. 4). BIG3 is pri marily expressed in pancreatic islets and the brain, and is found colocalized with lysosomes in neurons. BIG3 KO mice demonstrate increased $GABA_A$R syn aptic size and current, suggesting this protein is involved in negative regulation of $GABA_A$R levels (Liu et al., 2016). The exact role of specific $GABA_A$R subunits, associated E3-ligases and ubiquitination patterns, and lysosomal trafficking proteins that regulate the transition of surface receptors to lysosomes is an important area of future research.

ACTIVITY-DEPENDENT PLASTICITY OF $GABA_A$R SYNAPSES

Synapse plasticity refers to strengthening or weaken ing of individual synapses in response to changes in stimuli at a local or system level. Two decades of research have uncovered various forms of short and long term plasticity of GABAergic neurotransmission in different brain regions, with underlying cellular and molecular mechanisms being identified both preand post-synaptically (reviewed in (Flores and Méndez, 2014)). Persistent changes in synaptic efficacy are generally referred to as long-term potentiation (LTP) and long-term depression (LTD). Traditionally this described excitatory synapse plastic ity that produced a respective increase or decrease in synapse strength. However, with growing awareness of GABAergic synapse plasticity, these terms now refer to changes in the gain of either synapse type (for GABAergic synapses, iLTD and iLTP). Although changes in presynaptic efficacy of inhibitory synapses are well characterized and an important part of plastic ity (reviewed in Castillo et al., 2011; Castillo, 2012), here we will focus on postsynaptic cell-based plasticity mechanisms related to GABAAR trafficking.

$GABA_A$R postsynaptic plasticity is encompassed by changes in channel function, receptor number or clustering/lateral diffusion, and altered chloride homeostasis (changing the GABA reversal potential/E_{GABA}) (Fig. 5). Tonic inhibition generated by extrasynaptic receptors is also dynamic, with acute and chronic stress inducing changes in cell surface trafficking and subunit specific expression (reviewed in Maguire, 2014). Receptor phosphorylation state is a key means for altering channel function or receptor trafficking via activation of protein kinases (including PKC, PKA, CaMKII, and Src) or phosphatases (CaN, PP1, PP2A) (Fig. 5) (reviewed in Nakamura et al., 2015). Investigation of GABAergic postsynaptic plasticity has largely focused on excitation driven changes. Early plasticity studies identified that intra cellular application of CaMKII (Wang et al., 1995) and experimental epilepsy kindling models (Nusser et al., 1998) elevated $GABA_A$R surface levels and potentiated the inhibitory response. Later studies revealed that moderate NMDA activation of hippo campal neurons promote CaMKIIα translocation to inhibitory synapses and CaMKIIα-dependent inser tion of $GABA_A$Rs with concomitant phosphatase mediated AMPAR (GluR1) removal (Marsden et al., 2007, 2010). Aside from NMDAR stimulation, enhanced VGCC activity promotes CaMKII phos phorylation of the $\beta 3$ subunit S383 residue and receptor insertion (Fig. 4) (Saliba et al., 2012), suggesting multiple routes for calcium signaling to enhance $GABA_A$R surface levels. In addition, a quantum dot single-particle tracking study showed that NMDAinduced iLTP required CaMKII phosphorylation of $\beta 3$ S383 to reduce $GABA_A$R lateral diffusion and enhance recruitment of the synaptic scaffold protein gephyrin (Petrini et al., 2014). More recently, this experimental approach revealed

additional gluta mateand calcium-evoked plasticity of GABAergic synapses. Low glutamate levels stimulate mGluRdriven calcium store release via PKC and IP3 recep tors and stabilization of surface $GABA_A$Rs, while robust NMDAR activation promoted CaN phosphatase activity and destabilization of postsynaptic $GABA_A$R (Bannai et al., 2015). This is consistent with earlier findings where glutamate application pro motes CaMKIIα translocation to excitatory synapses, enhanced AMPAR surface levels, and reduced plasma membrane $GABA_A$R levels (Marsden et al., 2007, 2010). Glutamate, high levels of neuronal activity, or strong NMDAR activation also reduces plasma membrane $GABA_a$R cluster size, stimulates receptor lateral mobility, and decreases mIPSC amplitude via CaN (Bannai et al., 2009) and dephos phorylation of the γ2 subunit S327 residue (Fig. 3) (Muir et al., 2010). These molecular studies in neuro nal culture are consistent with earlier slice and *in vivo* studies showing LTD of GABAergic inhibition via NMDAR activation requires CaN (Lu et al., 2000) and the γ2 subunit (Wang et al., 2003). Similar mechanisms for iLTD and iLTP that rely on $GABA_A$R trafficking are supported by studies in other brain regions such as the deep cerebellar nuclei (Morishita and Sastry, 1996; Ouardouz and Sastry, 2000). Together these plasticity studies show that glutamate receptor activation and calcium-sensitive signaling pathways can generate either iLTP or iLTD. Moderate or ambient glutamate signaling promotes kinase activity that stabilizes $GABA_A$Rs, while strong stimulation leads to CaN phosphatase activation and receptor diffusion. Ultimately, glutamatergic activity dictates bidirectional modulation of GABAergic postsynaptic strength and receptor clustering.

Structural reorganization of gephyrin scaffolding is now emerging as a key mechanism of rapid inhibitory synaptic plasticity with changes occurring on a minute timescale (Specht et al., 2013). Gephyrin posttranslational modifications (described earlier) such as phosphorylation and ubiquitination are likely to be central in regulating synapse architecture. A recent organotypic slice culture study of gephyrin dynamics identified that activity patterns promoting NMDAR LTP (carbachol treatment or theta burst stimulation) increase gephyrin cluster size and formation in a CaMKII-dependent manner (Flores et al., 2015). Fur thermore this gephyrin plasticity was associated with enhanced phosphorylation of gephyrin S305, a CaMKII phospho site identified by *in vitro* kinase assay.

The critical role of CaMKII in $GABA_A$R synaptic plasticity is also seen in other brain regions. For example, rebound potentiation (RP), a cerebellar form of iLTP that follows Purkinje cell (PC, principal output neurons of cerebellum) depolarization, requires CaMKII activation (Kano et al., 1996) and increased association between the γ2 subunit and GABARAP (Kawaguchi and Hirano, 2007). RP relies on CaMKII recruitment of β2 containing receptors to the cell surface and occurs only on basket cell interneuron-PC soma synapses and not on stellate interneurons-distal PC dendrite synapses (He et al., 2015). This synapse specific potentiation by CaMKII is consistent with its ability to selectively increase β2-containing $GABA_A$Rs and mIPSC amplitude (Houston et al., 2008). Together this indicates two levels of selectivity based on input and subunit com position, as β2 containing synapses are also expressed on dendrites.

At the other end of the neuronal activity spectrum, early studies using chronic activity blockade (24–48 h TTX treatment) resulted in homeostatic preand post-synaptic GABAergic

plasticity with decreased $GABA_AR$ synaptic clusters, mIPSC amplitude and frequency (Kilman et al., 2002). *In vivo* chronic sen sory deprivation via whisker trimming decreases $GABA_AR$ number and weakens inhibitory synapses (Micheva and Beaulieu, 1995; Fuchs and Salazar, 1998; Gainey et al., 2016). In contrast, whisker train ing promotes GABAergic synaptogenesis on den dritic spines, while not on dendritic shafts (Jasinska et al., 2010). Analogous findings in the visual cortex (Chen et al., 2012) indicate that a pool of dynamic GABAergic spine synapses support changes to net work activity levels. These chronic *in vivo* protocols reveal how neuronal adaptation operates across a continuum of $GABA_AR$ synaptic plasticity, where reductions in activity lead to loss of inhibition, while learning or heightened neuronal activity strengthens existing GABAergic synapse or initiates new synapse formation. However, some sensory modulation can occur in an inverse fashion, as brief monocular depri vation potentiates iLTP (Maffei et al., 2006), concur rent with increasing gephyrin and $GABA_AR$ perisomatic accumulation (Petrini et al., 2014). Other visual cortex studies indicate that $GABA_AR$ endocy tosis contributes to LTD occurring with repetitive fir ing, while slow membrane oscillations, comparable to activity during sleep state, promote iLTP via exocytosis (Kurotani et al., 2008). Similarly, acquisition of a fear response is accompanied by surface $GABA_AR$ decreases (Chhatwal et al., 2005) and extinction of fear requires $GABA_AR$ insertion and GABARAP-receptor interaction (Lin et al., 2009). Parallel homeostatic changes are observed at excit atory synapses of interneurons, where increased net work activity also promotes interneuron excitability and mEPSC amplitude. However, we currently are not aware of studies examining homeostatic plasticity of GABAergic synapses on inhibitory interneurons. Collectively, GABAergic synapse plasticity and rewiring is fundamental for sensory experience adap tation, with functional changes in inhibition matching structural changes.

Homeostatic changes in $GABA_AR$ currents also occur through shifts in chloride homeostasis and GABA reversal potential (E_{GABA}). Studies in youn ger neurons with depolarizing and excitatory GABA show network activity blockade of voltage-gated sodium (Na) channels results in an increase in ampli tude of mPSCs via chloride accumulation and a depo larizing shift in the GABA reversal potential (Gonzalez-Islas et al., 2010; Lindsly et al., 2014). During development, regulated changes in intracellu lar chloride levels control receptor subunit composi tion in cerebellar neurons, tuning inhibition (Succol et al., 2012). Specifically, increased KCC2 levels and activity lead to a decrease in $\alpha 3$ subunits, while $\alpha 1$ and δ subunit expression increases. It remains to be shown whether changes in chloride homeostasis in the adult brain regulate subunit expression and recep tor composition in a similar fashion. KCC2 overex pression can switch the GABA response polarity to inhibition in young neurons (Lee et al., 2005), and conversely, downregulation of KCC2 surface levels by glutamate application abolished normal hyperpolarizing GABAergic inhibition in mature neurons (Lee et al., 2011). Interestingly, NL2 precedes KCC2 expression in development, and NL2 appears to promote KCC2 expression and the GABA switch from excitatory to inhibitory signaling as well as main tain GABA inhibition in mature neurons (Sun et al., 2013). Aberrant chloride homeostasis is an important contributor to the pathology of neuronal injury (reviewed in De Koninck, 2007; Kaila et al., 2014) including spinal cord injury, neuropathic pain ische mia, and traumatic brain injury. Furthermore, pertur bation or loss of the normal developmental GABA shift occurs in mouse models of

neurodevelopmental disorders including Down syndrome (He et al., 2014; Contractor et al., 2015; Deidda et al., 2015).

In summary, plasticity provokes many questions from the synapse to cell to circuit level. Clearly, due to the large number of overlapping trafficking regula tors, protein localization to excitatory or inhibitory synapses within a neuron is central to achieve specif icity and avoid producing overall synonymous changes at both synapse types. What are the distinct mechanisms occurring in pyramidal cells, interneur ons and interneuron subtypes? How is cell regionspecific plasticity achieved? To what degree does synapse-specific plasticity modulate circuit output? At the organism level, how do experience, drug expo sure or natural stimuli produce discrete patterns to appropriately modify inhibitory neurotransmission? A key step in achieving this local or populationbased plasticity may be through modulating $GABA_AR$ synapse development and trafficking by endogenous neuropeptides and neurosteroids.

NEUROPEPTIDE AND NEUROSTEROID MODULATION

Brain-Derived Neurotrophic Factor

The brain-derived neurotrophic factor (BDNF) protein plays a critical role in neurogenesis, neuroplas ticity, and neuroprotection. Knockout of the cognate BDNF target tropomyosin receptor kinase B (TrkB) disrupts GABAergic synaptogenesis in the cerebel lum (Rico et al., 2002). Furthermore, single-cell con ditional deletion of BDNF in the cortex causes a decrease in inhibitory postsynaptic currents and the number of GABAergic synapses onto pyramidal neu rons lacking BDNF (Kohara et al., 2007). The spe cific localization of BDNF/TrkB signaling is critical for this signaling pathway's role in synaptogenesis, as genetic ablation of BDNF-expressing cells in the internal granular layer of the cerebellum did not affect GABAergic synapse maturation, while selec tive deletion of BDNF from glutamatergic axons aris ing from distant precerebellar nuclei/spinal cord mossy fibers did (Chen et al., 2016). During neuronal development of cultured cerebrocortical neurons, excitatory, depolarizing $GABA_AR$ activity regulates a positive feedback loop by controlling secretion of BDNF, activation of TrkB and phosphatidylinositol 3-kinase (PI3K) and PKC activity, and reduction in receptor internalization (Porcher et al., 2011). Additionally, immature cultured hippocampal neurons demonstrated enhanced expression of gephyrin, gephyrin-α1 interaction, and $GABA_AR$ association at synapses following exogenous BDNF application (Gonzalez, 2014). Contrasting with BDNF enhance ment of GABAergic signaling early in development, acute exposure of BDNF in mature cultured hippo campal neurons enhanced receptors at the cell surface within 5 min, but decreased $GABA_AR$ current, func tion, and surface levels around 30–60 min (Brunig et al., 2001; Jovanovic et al., 2004). Accordingly, enhanced phosphorylation of the β3 subunit S408/409 sites by PKC occurred during initial BDNF treat ment, while longer exposure caused recruitment of protein phosphatase 2A (PP2A), β3 dephosphoryla tion, and endocytosis (Jovanovic et al., 2004). In a similar mature hippocampal paradigm, 15 min BDNF treatment led to a reduction in mIPSC amplitudes and long-lasting reduction of $GABA_AR$ levels up to 12 h (Brunig et al., 2001). In agreement with these find ings, hippocampal and amygdala neurons treated for 5–20 min with BDNF had a reduction in a1-$GABA_AR$ surface levels *in vitro*

(Mou et al., 2011). Gephyrin levels are also dynamically altered in the amygdala following BDNF, where 20 min exposure decreased the gephyrin pool, while a more chronic treatment lead to an increase (Mou et al., 2013).

In contrast, 2 h BDNF treatment in intact acute prefrontal cortical slices from adult mice enhances phosphorylation of the γ2-$GABA_AR$ subunit Y365/367 residues and causes long term stabilization of receptor surface levels (Vithlani et al., 2013). Inter estingly, hippocampal neurons derived from PRIP1/2 knockout mice demonstrate enhanced β3-phosphorylation and GABAergic current strength in response to BDNF. PRIP is required for the recruit ment of the phosphatase PP2A to $GABA_AR$ β- subunits (Fig. 4) (Kanematsu et al., 2006). Thus, BDNF treatment may be favoring PKC activity and phosphorylation of β subunits, an effect that would deter internalization, but can be offset by phosphatase activity. Additionally, BDNF regulates $GABA_AR$ subunit expression at the gene level in response to seizure paradigms *in vitro* and *in vivo* (Lund et al., 2008). BDNF acts to downregulate α1 subunit expression following pilocarpine-induced status epilepticus via a JAK/STAT signaling mechanism (Lund et al., 2008), while enhancing α4 subunit levels via an early growth response factor 3 (Egr3)/MAPKdependent pathway (Roberts et al., 2005, 2006).

Although early depolarizing $GABA_AR$ signaling promotes neuronal maturation (Ben-Ari et al., 20l2), growing evidence suggests that BDNF signaling can promote transient excitatory (or diminished inhibi tory) $GABA_AR$ signaling following noxious stimuli or injury. Adult cats who receive BNDF treatment following a unilateral vestibular neurectomy, a proce dure reported to enhance reactive cell proliferation in the vestibular nucleus and recovery following CNS injury (Tighilet et al., 2007), demonstrate accelerated functional recovery associated with decreased KCC2 and increased $GABA_AR$ levels (Dutheil et al., 20l6). A BDNF/TrkB-dependent depolarizing shift in E_{GABA} also occurs pre-synaptically following nerve injury in the spinal cord that reduces presynaptic inhibition and contributes to the initiation of neuro pathic pain (Chen et al., 20l4).

Importantly, the non-cleaved BDNF precursor, proBDNF, binds a separate receptor known as $p75^{NTR}$, and was found to stimulate $GABA_AR$ β3 subunit dephosphorylation via the RhoA-ROCK-PTEN path way. As a result, $GABA_AR$ internalization was enhanced, surface and total levels were reduced, and GABAergic neurotransmission was dampened (Rif-fault et al., 20l4). These findings were confirmed by *in vivo* work using P0 rats given intracerebroventricular injections of tPA-Stop, an inhibitor of plasminogen causing accumulation of proBDNF, producing decreased β3 subunit phosphorylation, and reduced mIPSC amplitude and frequency. Neuronal expression of a non-maturable version of proBDNF abolished the excitatory to inhibitory shift of GABA and reduced KCC2 levels in the cortex (Riffault et al., 20l6). Simi larly, interfering with early depolarizing GABA in newborn mice using the NKCCl-blocker bumetanide prolonged the critical period of postnatal development in the visual cortex and led to long-term reductions in inhibitory tone and BDNF expression without a change in visual function (Deidda et al., 20l5). Accordingly, co-treatment of the BDNF mimetic drug 7,8-dihydroxyflavonone reversed the deficiencies in plasticity induced by bumetanide treatment. Over all, the experimental and brain-region dependent responses to BDNF and its precursors highlight the specific and diverse role of this protein in regulation of $GABA_AR$ function and plasticity.

Insulin

Circulating hormones involved in basic metabolic and energy balance are important for neuronal development and stability. The major role of insulin in regulating $GABA_AR$ synaptic (Wan et al., l997) and surface levels (Mielke and Wang, 2005) is well described in a previous review (Luscher et al., 20lla). In summary, insulin acts to promote rapid forward trafficking of newly synthesized $GABA_ARs$ from the ER and Golgi via an—AKT/PRIP depen dent pathway and $GABA_AR$ β subunit phosphoryla tion (S409 in β1, S4l0 in β2, S408/409 in β3) (Fig. 4) (Wang et al., 2003; Xu et al., 2006; Fujii et al., 20l0). A PI3K pathway is also involved in increased $GABA_AR$ phospholipid interactions following insulin exposure (Vetiska et al., 2007). A role for aberrant insulin signaling and $GABA_AR$ trafficking in ASD was recently described for individuals carrying the MET tyrosine kinase receptor risk allele (Lo et al., 20l6). Conditional mutant mice expressing kinase-dead Met restricted to hippocampal and cortical regions demonstrate an enhanced excitatory/inhibi tory ratio, loss of postsynaptic inhibition, and resis tance to insulin-induced enhancements in the strength of GABAergic neurotransmission.

Neurosteroids and Oxytocin

Neurosteroids act at most $GABA_AR$ subtypes and can both enhance or inhibit GABAergic neurotransmis sion. 3a-hydroxy A-ring reduced metabolites of pro gesterone, deoxycorticosterone, and testosterone are positive allosteric modulators of specific $GABA_ARs$ (notably, allopregnanolone or 3α,5α-tetrahydroprogesterone [THP] and tetrahydro-deoxycorticosterone [THDOC]). In contrast, 3β-OH pregnane steroids and pregnenolone sulfate are $GABA_AR$ antagonists. Neu rosteroids which enhance receptor activation have binding sites at the α subunit and the β-α subunit interface, while the δ subunit does not affect initial binding but enhances the efficacy of potentiation (Hosie et al., 2009). For instance, THP and THDOC shift GABA activation from partial to full agonism at δ-containing receptors (Wohlfarth et al., 2002; Bianchi and Macdonald, 2003; Zheleznova et al., 2008). The δ subunit is important for the physiological response to neurosteroids, as mice deficient of this subunit have attenuated responsiveness to the behav ioral and $GABA_AR$ modulatory effects of these agents (Mihalek et al., l999; Boehm et al., 2006; Shen et al., 20l0).

Surface expression of $\alpha4\beta\delta$ $GABA_ARs$ is highly plastic in response to neuroactive steroids including THP (Shen et al., 2005), THDOC (Stell et al., 2003; Comenencia-Ortiz et al., 20l4), progesterone and its metabolite allopregnanolone. Several *in vivo* studies show steroids can robustly enhance total levels of the α4 and δ subunit (Gulinello et al., 2001; Hsu et al., 2003; Maguire and Mody, 2007). Accordingly, marked changes in circulating levels of neuroactive steroids that occur during the estrous cycle (Lovick et al., 2005; Maguire et al., 2005; Carver et al., 2014), puberty (Shen et al., 2007), pregnancy (Sanna et al., 2009), and post-partum (Maguire and Mody, 2008) ultimately fine-tune $GABA_AR$ inhibitory neu rotransmission (Maguire and Mody, 2009). Additional alterations of neurosteroids have been identified in seizure susceptibility (Tan et al., 2015; Joshi et al., 2017), social isolation behavior in mice (Agis-Balboa et al., 2007), and in the cerebrospinal fluid of humans with depression (Romeo et al., 1998) and post-traumatic stress disorders (Rasmusson et al., 2006). Localization of receptors and the release site of endogenous neurosteroids may also

impact func tional neurosteroid effects. For instance, mice sub jected to temporal lobe epileptic seizures show increased synaptic $\alpha 4$ levels and insensitivity to allopregnanolone in mIPSC slice recordings of dentate granule cells (Sun et al., 2007). It is unclear if this change in responsiveness to neurosteroids is strictly due to $\alpha 4$ receptor synaptic association or a broader byproduct of the dramatic changes in cellular func tion and toxicity incurred by seizure events. The local production of neurosteroids also has an important developmental role in fine-tuning thalamic neuron transitions from relatively slow to fast phasic signal ing (Brown et al., 2015).

Neurosteroids act to enhance extrasynaptic recep tor surface levels by influencing the phosphorylation status of $GABA_AR$ subunits. For example, THDOC exposure enhances PKC-mediated phosphorylation of the $\alpha 4$ subunit S443 site leading to receptor inser tion and increased tonic current (Abramian et al., 2010, 2014), while also enhancing PKC-mediated phosphorylation of $\beta 3$ subunit S408/409 residues (Adams et al., 2015). Acute hippocampal slices treated with allopregnolone or the synthetic neuroste roid SGE-516 also demonstrate enhanced S408/409 phosphorylation and increased total $\beta 3$ subunit sur face levels, although these two agents had distinct effects on spontaneous IPSC amplitude (Modgil et al., 2017). Modifying PKA and PKC activity in HEK293 cells alters the sensitivity of both synaptic $\alpha 1\beta 3\gamma$ and extrasynaptic $\alpha 4\beta 3\delta$ responsiveness to THDOC potentiation (Adams et al., 2015). Alanine mutation of $\beta 3$ S408/409 sites diminished potentia tion of synaptic receptors to THDOC, while triple mutant $\alpha 4^{S443A}\beta 3^{S408A,S409A}\delta$ receptors were required to yield the same insensitivity to changes in broad spectrum kinase inhibition by staurosporine, suggesting phosphorylation of both subunits is required for neurosteroid regulation of extrasynaptic receptors (Adams et al., 2015). Kindling and broad activation of PKC by the phorbol ester PMA also reduces responsiveness to THDOC in temporal lobe rat slices (Kia et al., 2011), suggesting overlapping mechanisms of action at $GABA_ARs$. Neurosteroids may also play a role in the ethanol-induced increase in $\alpha 4$ subunit levels (Shen et al., 2012) and intake behavior (Rewal et al., 2009), possibly explaining high sensitivity to THDOC during alcohol with drawal (Devaud et al., 1996).

The neuropeptide oxytocin, commonly associated with childbirth and breastfeeding, also enhanced pro tein expression of extrasynaptic $GABA_AR$ $\alpha 4$ and δ subunits in a mixed neuronal/astrocyte primary cell preparation (Kaneko et al., 2016). This effect of oxyto cin increased responsiveness to THIP in electrophysiological recordings and provided neuroprotective effects against oxygen-glucose deprivation treatment. Interestingly, the oxytocin receptor (Oxtr) has also been implicated as a regulator of the excitatory to inhibitory switch of $GABA_AR$ function by controlling KCC2 activity (Leonzino et al., 2016). Developmental upregulation of KCC2 function and surface stability through phosphorylation is carefully regulated by Oxtr signaling, and thus mice lacking Oxtr have reduced phospho-KCC2, enhanced excitatory/inhibitory ratio, and seizure susceptibility. Collectively, neurosteroid and neuropeptide signaling dynamically fine-tune $GABA_AR$ activity, but their mechanistic role in regu lating homeostatic $GABA_AR$ trafficking and expres sion remains to be fully elucidated.

TECHNICAL ADVANCEMENTS AND FUTURE OUTLOOK

Considerable scientific progress has revealed a net work of molecular mechanisms underlying GABAer-gic plasticity (Fig. 5). Yet, advancement of new and existing methods is promoting major inroads for our understanding of $GABA_AR$ signaling and trafficking. Recent proteomic strategies have vastly expanded the protein repertoire of GABAergic synapses to nearly 200 proteins by targeted purification of $GABA_ARs$, NL2, or gephyrin (collybistin and InSyn1 to a lesser extent) and their respective interactomes (Kang et al., 2014; Loh et al., 2016; Nakamura et al., 2016; Uezu et al., 2016). Microscopy-based approaches encom pass the fastest growing means of discovery *in vitro* and *in vivo*, including optogenetically controlled $GABA_ARs$ (Lin et al., 2014, 2015), two-photon based GABA photolysis (Oh et al., 2016), single-particle-tracking of receptor diffusion (Petrini and Barberis, 2014), quantitative super-resolution imaging of gephyrin (Pennacchietti et al., 2017) and gephyrin recombinant antibody-like proteins (Gross et al., 2013, 2016) or fluorescent super-binding peptides (Maric et al., 2017). Additionally, proximity ligation assays allow for researchers to detect native protein interactions utilizing widely-available primary anti bodies (Smith et al., 2014; Tseng et al., 2015), while emerging single-molecule fluorescence resonance energy transfer methods (smFRET) have yet to be applied. When considering these advancements in parallel with the rise of modern clinical genomics like human exome sequencing (Myers and Mefford, 2015; Yuan et al., 2015; Wang et al., 2017), the dis covery rate and resolution of GABAergic mediators applicable to human health and disease is primed to accelerate exponentially.

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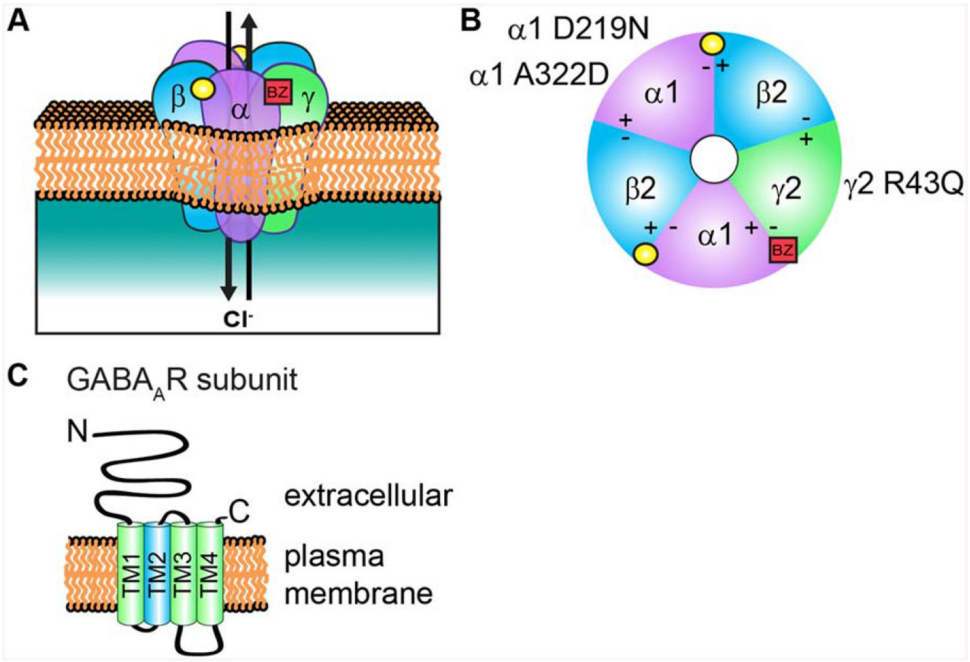

Figure 1.

$GABA_aR$ structure and subunit topology. (**A**) A representation of the heteropentameric $GABA_AR$ composed of $\alpha\beta\gamma$ subunits. Binding of the neurotransmitter GABA (yellow circle) at the $\alpha\beta$ interface triggers ion channel opening and allows the rapid influx of Cl^- and membrane hyper polarization in the mature nervous system. (**B**) Extracellular representation of the receptor showing all five subunits contributing to the central ion pore and the general binding sites of GABA (yellow circle) and BZs (red square). BZs bind at the interface of an α1/2/3/5 and y subunit. Also shown are specific mutations in a and γ2 subunits discussed in this review that contribute to epilepsy disorders by disrupting receptor assembly and trafficking. (**C**) All subunits have a common topology includ ing an extracellular N-terminal domain, short C-terminal tail, and four transmembrane domains (TM1–4). $GABA_AR$ subunit TM2 (blue) contributes to formation of the receptor ion channel pore, while the intracellular loop between TM3 and TM4 contain sites of phosphorylation and protein interactions that modulate channel function and/or trafficking. [Color figure can be viewed at wileyonlinelibrary.com]

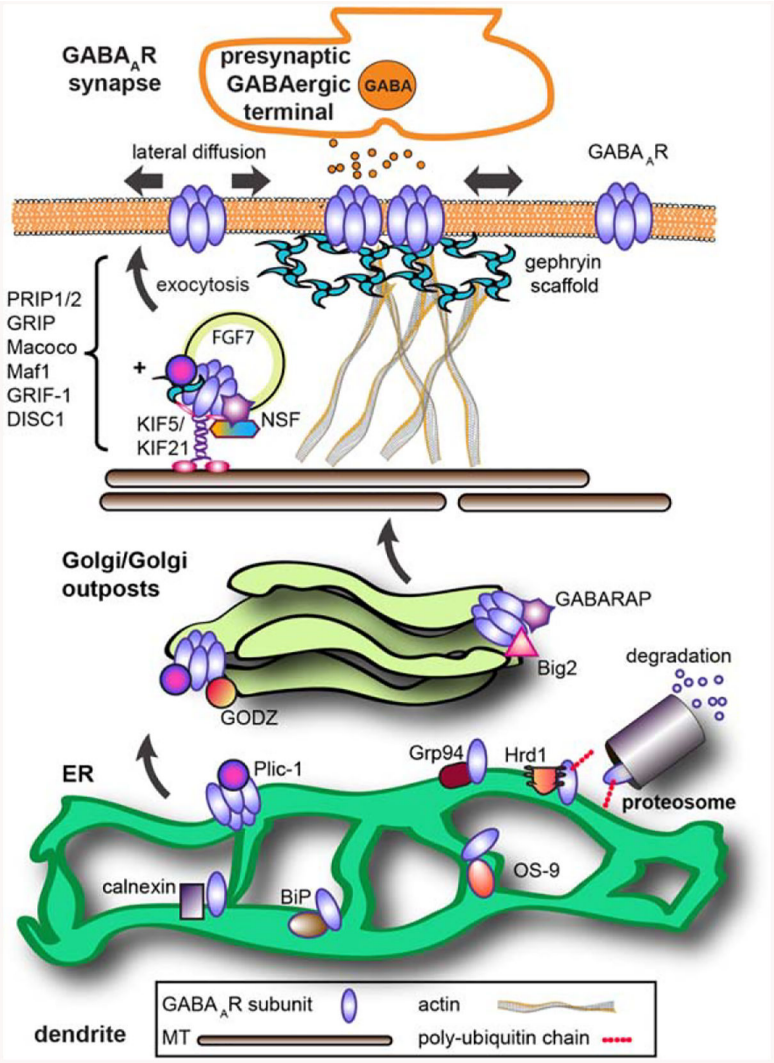

Figure 2.

Forward trafficking of $GABA_ARs$. The process of $GABA_AR$ synthesis, assembly and forward trafficking is highly of misfolding regulated. Subunit assembly into pentameric recep tors in the ER involves ER chaperones (BiP, calnexin). Identification (Grp94, OS-9) leads to E3 ligase (Hrd1) ubiquitination of receptors and their destruc tion in the proteasome. Plic-1 inhibits proteosomal degrada tion of receptors, facilitating receptor ER exit to the Golgi. In the Golgi, palmitoylation of y subunits by the palmitoyl transferase GODZ is a key step in promoting forward traf ficking to the synapse. The GTP exchange factor Big2 increases receptor exit from the Golgi. A large number of $GABA_AR$-associated proteins contribute to surface delivery of vesicles containing receptors from the Golgi. The kinesin KIF5 is the main microtubule-dependent motor transporting inhibitory synapse components (in addition to receptors this includes gephyrin, GABARAP, and FGF7) although recent work shows KIF21 contributes to extrasynaptic receptor delivery. Once inserted into the plasma membrane at extrasynaptic sites, receptors laterally diffuse until inter actions with the gephyrin scaffold enhance receptor synap tic accumulation. [Color figure can be viewed at wileyonlinelibrary.com]

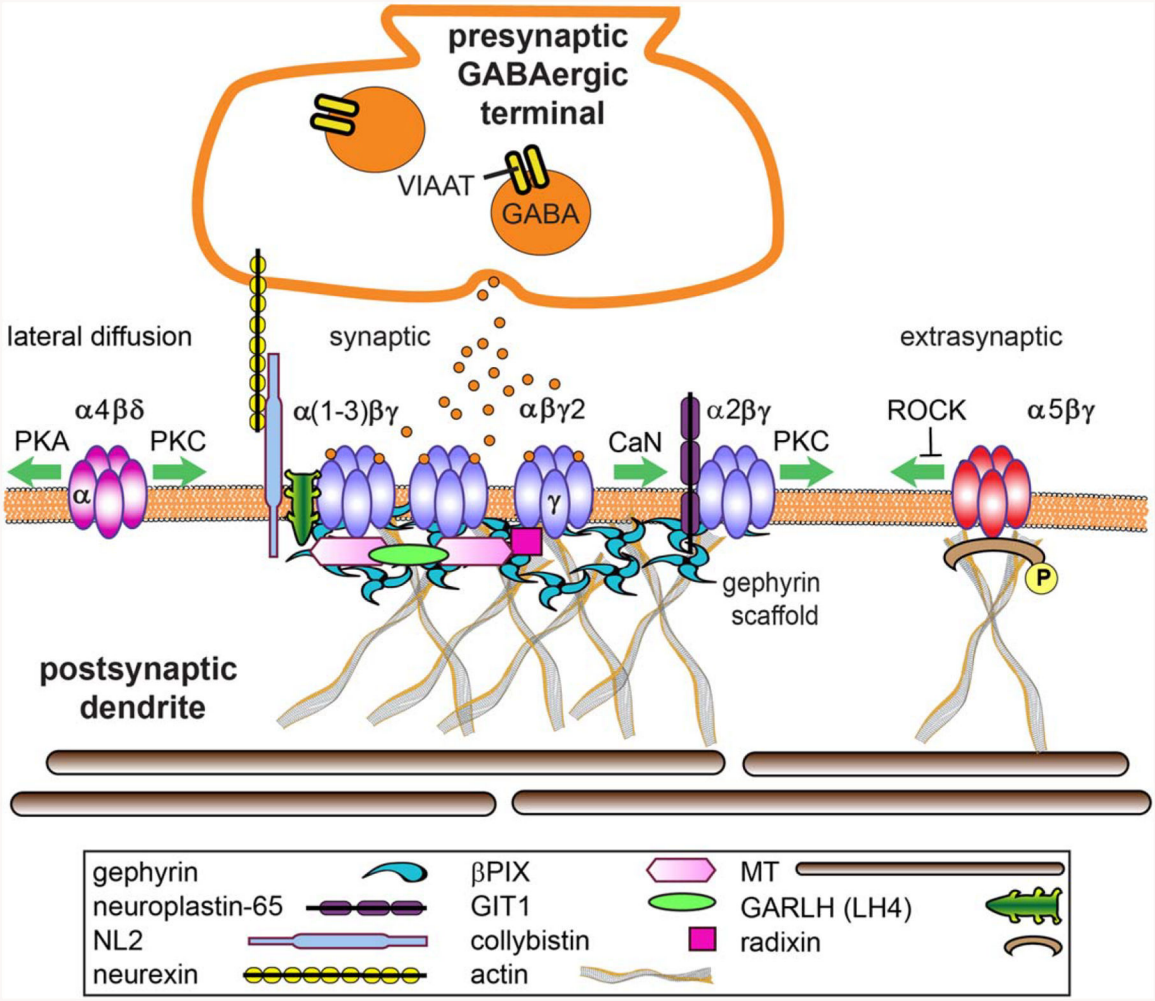

Figure 3.

$GABA_AR$ synapse structure. $GABA_ARs$ composed of α(1–3)$\beta\gamma$ subunits are largely synaptically localized via gephyrin interactions and contribute to phasic currents, whereas α(4 or 6)βd receptors are extrasynaptic and generate tonic current. $\alpha5\beta\gamma$ receptors are found in both locations due to binding with gephyrin at synapses and radixin extrasynaptically. Proteomics and other mod ern strategies have significantly enriched the complexity of the inhibitory synapse, however the functions of many new components have yet to be defined. Key synaptic adhesion, scaffold and sig naling proteins that mediate lateral diffusion of receptors in and out of the synapse are depicted and discussed in this review. [Color figure can be viewed at wileyonlinelibrary.com]

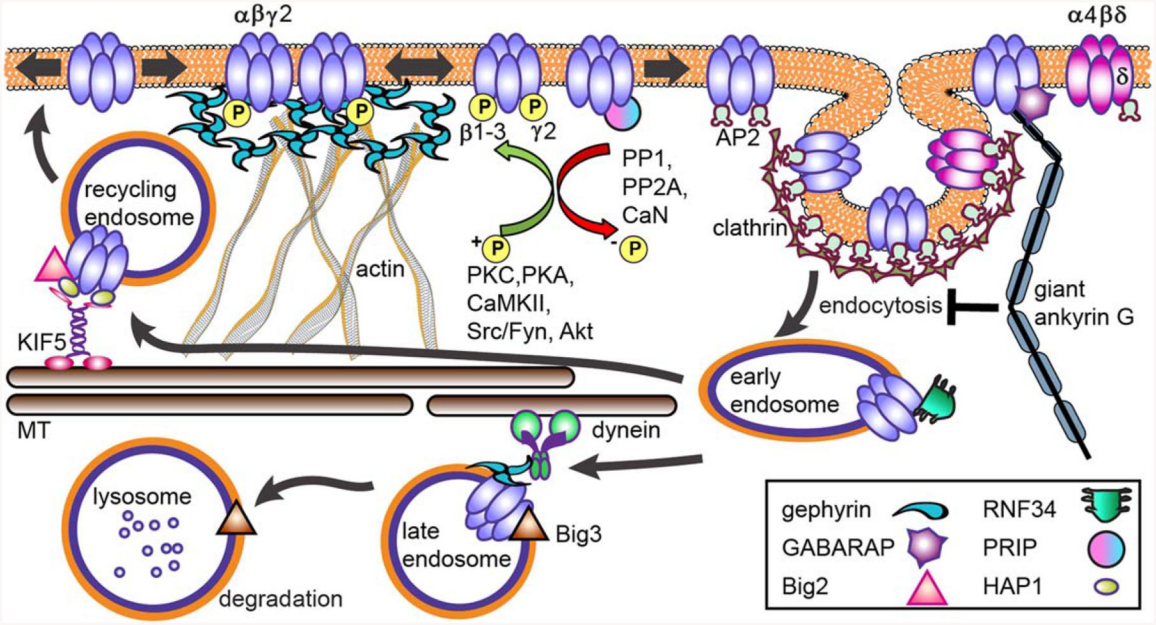

Figure 4.

$GABA_AR$ endocytosis, recycling and degradation. $GABA_ARs$ primarily undergo clathrin-dependent endocytosis. β, γ, and δ subunits interact with the clathrin-adaptor protein 2 (AP2) complex. Phosphorylation of AP2-interaction motifs within receptor subunits increases cell-surface receptor levels and enhances $GABA_AR$ neurotransmission. Giant ankyrin G, in addition to its scaffold function, negatively regulates $GABA_AR$ endocytosis. After internalization, clathrin-coated vesicles fuse with early endosomes, allowing for subsequent receptor recycling or targeting for degradation in lysosomes. HAP1 interaction with β subunits promotes receptor recycling. Ubiq uitination of $GABA_AR$ contributes to lysosomal targeting, with the ubiquitin E3 ligase RNF34 directly interacting with the $\gamma 2$ subunit. In contrast to the Arf GEF Big2 found on recycling endo-somes membranes, Big3 is colocalized with neuronal lysosomes and promotes receptor degrada tion. [Color figure can be viewed at wileyonlinelibrary.com]

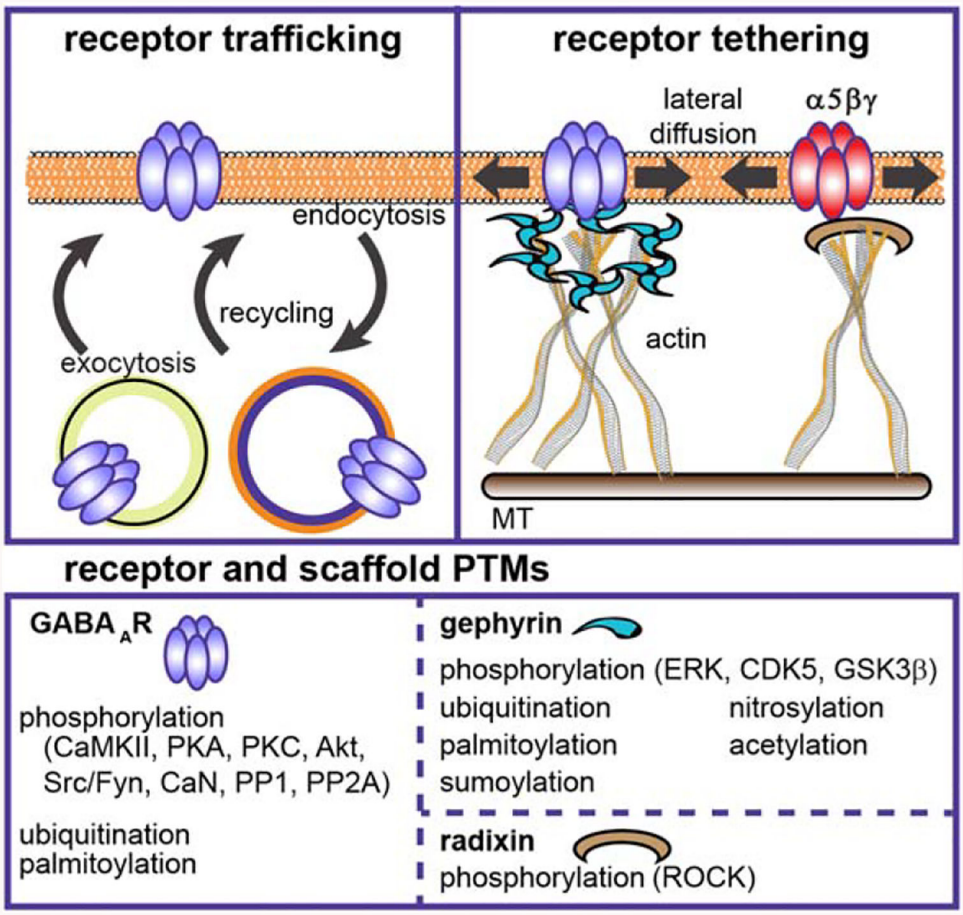

Figure 5.

GABAergic postsynaptic plasticity. Many forms of $GABA_AR$ plasticity rely on modulation of receptor traf ficking or tethering via scaffold interactions, including activity-dependent iLTP and iLTD. In addition to newly identified phosphorylation sites and signaling pathways, diverse post-translational modifications are surfacing as regulators of $GABA_AR$ trafficking processes, both at the level of receptors and scaffolding. [Color figure can be viewed at wileyonlinelibrary.com]