



GABA_A receptors: post-synaptic co-localization and cross-talk with other receptors

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γ -Aminobutyric acid type A receptors (GABA_ARs) are the major inhibitory neurotransmitter receptors in the central nervous system, and importantly contribute to the functional regulation of the nervous system. Several studies in the last few decades have convincingly shown that GABA can be co-localized with other neurotransmitters in the same synapse, and can be co-released with these neurotransmitters either from the same vesicles or from different vesicle pools. The co-released transmitters may act on post-synaptically co-localized receptors resulting in a simultaneous activation of both receptors. Most of the studies investigating such co-activation observed a reduced efficacy of GABA for activating GABA_ARs and thus, a reduced inhibition of the post-synaptic neuron. Similarly, in several cases activation of GABA_ARs has been reported to suppress the response of the associated receptors. Such a receptor cross-talk is either mediated via a direct coupling between the two receptors or via the activation of intracellular signaling pathways and is used for fine tuning of inhibition in the nervous system. Recently, it was demonstrated that a direct interaction of different receptors might already occur in intracellular compartments and might also be used to specifically target the receptors to the cell membrane. In this article, we provide an overview on such cross-talks between GABA_ARs and several other neurotransmitter receptors and briefly discuss their possible physiological and clinical importance.

Keywords: GABA_AR, cross-talk, ionotropic receptors, metabotropic receptors, targeting

INTRODUCTION

GABA (γ -aminobutyric acid) is the major inhibitory transmitter in the brain. Depending on the brain region, about 20–50% of all synapses use GABA as a transmitter. GABA, released from the pre-synaptic terminal can exert its action via two types of receptors, ionotropic GABA_A (GABA_ARs) and metabotropic GABA_B receptors (GABA_BRs). Most of the actions of GABA are mediated via GABA_ARs. These are chloride ion channels composed of five subunits that can belong to different subunit classes. In mammalian brain there are a total of 19 different subunits derived from 8 different subunit classes (6 α , 3 β , 3 γ , δ , ϵ , π , θ , 3 ρ), giving rise to a multiplicity of different GABA_AR subtypes with distinct subunit composition and pharmacology (Sieghart, 1995; Olsen and Sieghart, 2009). The majority of GABA_ARs, however, is composed of 2 α , 2 β , and 1 γ subunit. Like other neurotransmitter receptors,

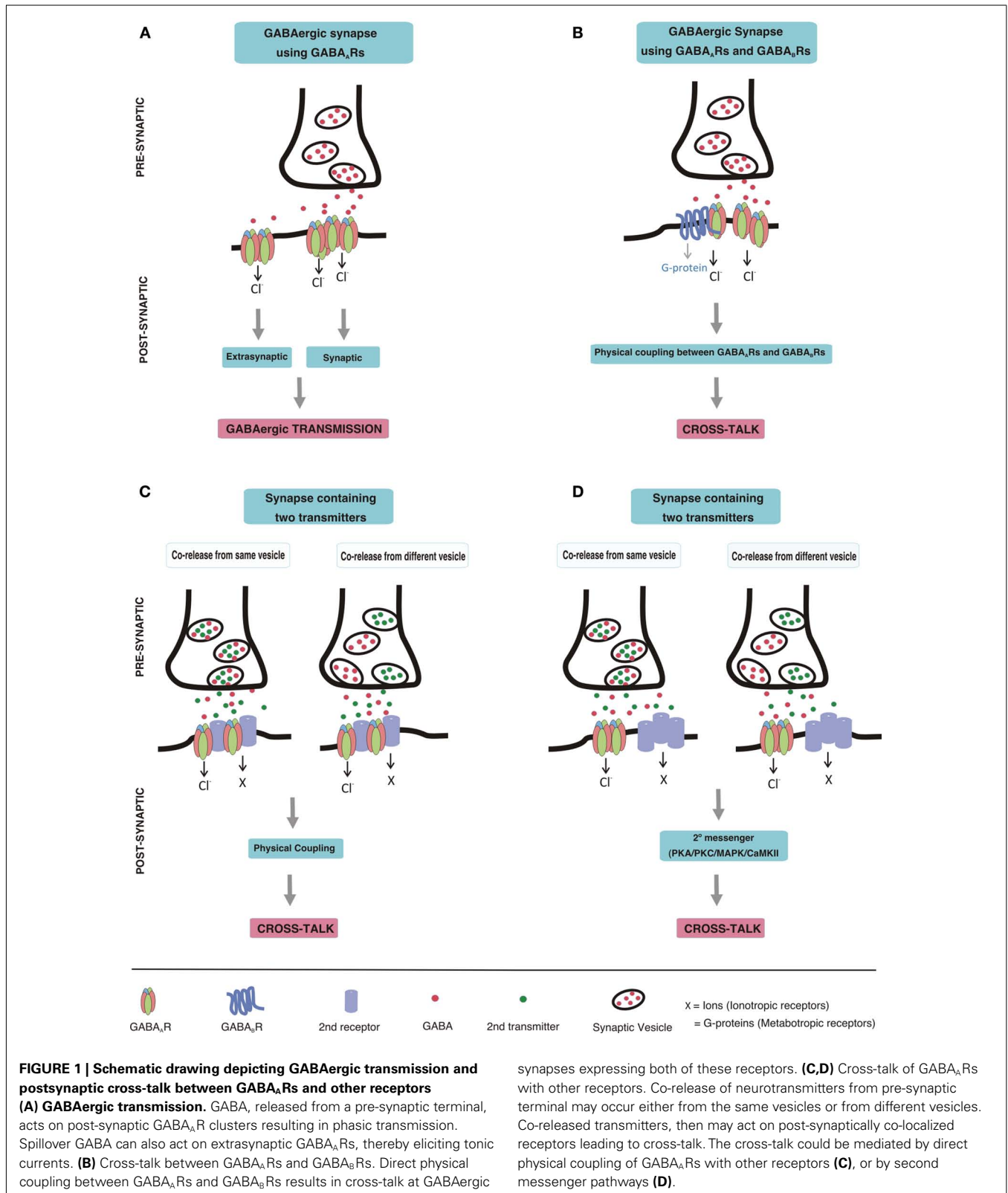
GABA_ARs are located at synapses as synaptic clusters (Moss and Smart, 2001; Renner et al., 2008; Bannai et al., 2009) where they are stabilized by scaffold proteins such as gephyrin (Kneussel et al., 1999; Tretter et al., 2008). Recent evidence, however, indicates that “clusters” of these receptors are also present at extrasynaptic locations (Lévi et al., 2008; Kasugai et al., 2010; Kneussel, 2010; Shrivastava et al., 2011). Synaptic as well as extrasynaptic clusters presumably consist of multi-molecular aggregates localized in the plane of the plasma membrane, which can contain not only multiple GABA_ARs and interacting proteins, but also other types of receptors. In fact, several of such interacting receptors from different transmitter classes have been described to be closely associated with GABA_AR clusters. Interestingly, most if not all of the studies addressing GABA_AR interactions with other receptors have observed a suppression of GABAergic inhibition upon co-activation of the associated receptors. Additionally, in several studies activation of GABA_ARs has been reported to suppress the response of the associated receptors. Such a functional inhibition of one receptor activity by activation of a second receptor is often termed as “cross-talk” between these receptors.

Here we summarize what is known on the post-synaptic co-localization and cross-talk of GABA_ARs with other receptors. Such a cross-talk can be mediated by a direct physical contact of the receptors and subsequent allosteric modulation of their properties on binding of the one, or the other, or of both ligands, by

Abbreviations: 5-HT₃Rs, serotonin type 3 receptors; A1, A2A, A2B, A3 receptors, adenosine receptors; AMPARs, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; CaMKII, Ca²⁺/calmodulin-dependent kinase II; D1-5 receptors, dopamine D1-5 receptors; GABA, γ -aminobutyric acid; GABA_ARs, GABA type A receptors; GABA_BRs, GABA type B receptors; GAD, glutamic acid decarboxylase; GlyR, glycine receptors; IPSC, inhibitory post-synaptic currents; MAPK, mitogen-activated protein kinase; nAChRs, nicotinic acetylcholine receptors; NMDARs, N-methyl-D-aspartate receptors; P2XRs, purinergic P2X receptors; PKA, protein kinase A; PKC, protein kinase C; VGAT, vesicular GABA transporter; VGLUT, vesicular glutamate transporter.

indirect modulation of receptor properties via a second messenger system activated by the associated receptor, or by both mechanisms together. A more remote interaction between different receptors,

in which one receptor modulates the release of the transmitter activating the other receptor, will not be systematically considered in this review, because each receptor located pre-synaptically can



modulate the release of a transmitter. It only will be mentioned when a possible additional direct cross-talk between a receptor pair seems to exist. Furthermore, modulation of GABAergic transmission by second messenger mechanisms elicited via other synapses will also not be discussed here, because many receptors located in the post-synaptic neuron can cause such modulation. Accordingly, we use the following criteria as supportive arguments for receptor cross-talk: (i) their neurotransmitters are either co-released or can simultaneously interact with both receptors at the post-synaptic membrane, (ii) the receptors are co-localized in certain synapses of the brain, (iii) they physically interact with each other (iv) simultaneous activation of the two receptors produces a non-additive current (current occlusion; Figure 1).

The review has been split into the following chapters to separately address individual receptor pairs:

- i Cross-talk of GABA_A with GABA_B receptors
- ii Cross-talk of GABA_A with glycine receptors
- iii Cross-talk of GABA_A with nicotinic acetylcholine receptors
- iv Cross-talk of GABA_A with serotonin receptors
- v Cross-talk of GABA_A with dopamine receptors
- vi Cross-talk of GABA_A with purinergic P2X receptors
- vii Cross-talk of GABA_A with adenosine receptors
- viii Cross-talk of GABA_A with NMDA receptors

CROSS-TALK OF GABA_A WITH GABA_B RECEPTORS

Pre-synaptically released GABA not only acts on GABA_ARs but also on GABA_BRs. GABA_BRs are metabotropic G-protein coupled receptors, which exist as heteromers of GABA_{B1} and GABA_{B2} subunits (Schwenk et al., 2010). These receptors are localized both pre- and post-synaptically (Pinard et al., 2010). Several studies have demonstrated that activation of pre-synaptic GABA_BRs reduced post-synaptic GABAergic transmission by reducing GABA release (Deisz and Prince, 1989; Davies et al., 1991; Mott and Lewis, 1991; Kardos et al., 1994). Other studies, however, are consistent with an additional cross-talk of post-synaptic GABA_A and GABA_BRs. Immuno-localization studies in the basal ganglion of the human brain indicated that the GABA_Aα1-subunit and the GABA_{B1} subunit are co-localized on GABAergic striatal interneurons and on neurons in the globus pallidus and substantia nigra pars reticulata but not on those of substantia nigra pars compacta (Waldvogel et al., 2004). In addition, both receptors were found to be co-localized at symmetrical synapses and possibly also at extrasynaptic sites (Smith et al., 2001). Another study demonstrated a direct interaction of GABA_{B1} subunits with γ2S subunits of GABA_ARs in rat brain lysate (Balasubramanian et al., 2004) and results indicated that this subunit regulates GABA_BR trafficking in multiple ways. This study also demonstrated that GABA_{B1} subunit co-expression with GABA_ARs increased the potency of GABA for activating GABA_ARs.

In addition, earlier studies provide some evidence that the two receptors indeed exhibit cross-talk. Thus, Kardos et al. (1994), reported that the inhibitory action of GABA on K⁺-evoked glutamate release in cultured cerebral granule cells was similar to that observed by the concerted action of the GABA_AR agonist isoguvacine and the GABA_BR agonist, baclofen. Surprisingly this effect

was smaller than the sum of the inhibitory actions of isoguvacine and baclofen added separately. These results for the first time proposed that the two GABA receptors may functionally interact with each other in such a way that the final outcome results in a reduced inhibition (=disinhibition; Kardos et al., 1994; Schousboe, 1999). The functional inhibition of GABA_ARs by activation of GABA_BRs was additionally observed using Ca²⁺-imaging in developing hypothalamic neurons, in which GABA_ARs are excitatory and raise cytosolic Ca²⁺ level on activation. Dose-dependent administration of baclofen depressed GABA_AR-mediated Ca²⁺-influx in these cells (Obrietan and van den Pol, 1998). Although the authors confirmed a stronger involvement of pre-synaptic GABA_BRs on electrically evoked GABA release, they could additionally observe depression of muscimol-evoked GABA_AR-mediated Ca²⁺-influx by baclofen when blocking pre-synaptic activity by tetrodotoxin, suggesting a possible involvement of post-synaptic GABA_BRs too. Whether these effects were caused by a direct interaction of GABA_A and GABA_B receptors or by a second messenger mechanism, however, was not investigated.

These studies seem to indicate that pre-synaptically released GABA can act on post-synaptically co-localized GABA_A and GABA_BRs resulting in a reduction of GABAergic signaling. However, more studies have to be performed to understand the possible mechanism of this cross-talk. Additionally, whether GABA_AR can also suppress GABA_BRs mediated signaling, and whether any second messenger system is involved, still needs to be clarified. As GABA_BRs are highly abundant in the central nervous system (CNS), their simultaneous activation and cross-talk with GABA_ARs may play an important role in fine tuning of inhibition in the nervous system. Thus, it might limit hyperpolarization caused by excess of GABA release, and simultaneously overcome a failure of inhibition caused by a local change of the Cl⁻ reversal potential (Segal and Barker, 1984; Staley et al., 1995) by GABA_BR activated K⁺ channels.

CROSS-TALK OF GABA_A WITH GLYCINE RECEPTORS

Glycine receptors (GlyRs), like GABA_ARs, are members of the cys-loop receptor family and share the load of inhibition with GABA_ARs in the CNS. GlyRs are highly abundant in spinal cord, brain stem and retina, where GABA_ARs are also expressed. The neurotransmitters GABA and glycine are co-localized in many synapses, and can be co-released from them. Actually, co-release of GABA and glycine was demonstrated to occur from the same vesicle in interneuron–motoneurons synapses in spinal cord slices (Jonas et al., 1998). Co-release of GABA and glycine has additionally been reported in brain stem slice preparations at the hypoglossal motoneuron synapse (O'Brien and Berger, 1999) and the abducens motoneuron synapse (Russier et al., 2002). Other studies not only demonstrated the co-existence of GABA and glycine, but also a co-localization of GABA_ARs and GlyRs at synapses in spinal cord neurons (Triller et al., 1987; Bohlhalter et al., 1994; Todd et al., 1996; Shrivastava et al., 2011). Another recent study provided a quantitative estimate of such mixed GABAergic/glycinergic synapses (Lévi et al., 2008) suggesting that a substantial proportion of spinal cord inhibitory synapses house both of these inhibitory receptors.

Surprisingly, even before the co-release of these two neurotransmitters was demonstrated, a partial inhibition of the GABA response by glycine was reported in rat medullary neurons (Lewis and Faber, 1993). Later, Trombley et al. (1999), using whole-cell voltage clamp recordings, studied this in more detail in rat olfactory bulb neurons, where they observed that in the majority of these neurons, glycine inhibited GABA-evoked currents and GABA inhibited glycine-evoked currents. They additionally observed that on co-application of saturating concentrations of GABA and glycine to these neurons the current amplitude was less than the sum of the currents evoked by GABA and glycine alone, demonstrating current occlusion. Later, similar cross-inhibition was reported in neurons from rat sacral dorsal commissural nucleus (Li et al., 2003). The authors additionally observed that this cross-inhibition was asymmetric (GABA-evoked currents were more affected by glycine than glycine-evoked responses by GABA). In addition, it was reversible, and depended on the phosphorylation of GABA_ARs. This indicates that more complex signaling pathways might be involved in this cross-talk. Taken together, all these results suggest that the two receptors are in close proximity, but whether they also are physically interacting remains to be clarified.

Recent findings, however, offer alternative explanations for a possible cross-talk of GABA_ARs and GlyRs, that does not require direct physical interaction of these receptors. Thus, it has been demonstrated that at physiological concentrations GABA acts as an endogenous ligand (weak partial agonist) for synaptic GlyRs (Jonas et al., 1998; De Saint Jan et al., 2001; Lu et al., 2008; Singer, 2008). GABA thus not only activates GABA_ARs but also to a lesser extent GlyRs. The GlyR activation by GABA, however, would be gone as soon as glycine is simultaneously applied, resulting in non-additive effects. In addition it was reported that GlyRs activated by very high concentrations of GABA have deactivation times 10 times faster than receptors activated by glycine (Fucile et al., 1999). Thus, by directly activating GlyRs, GABA can narrow the time window for effective glycinergic inhibition (Lu et al., 2008) resulting in an additional mechanism of cross-talk of the GABAergic and glycinergic system. Finally, strong simultaneous activation of GABA_ARs and GlyRs could cause an increase of the local chloride concentration in the cell, thus reducing further chloride influx (Segal and Barker, 1984; Staley et al., 1995). Further experiments will have to analyze whether such mechanisms could explain the observed receptor “cross-talk.”

In any case, GABA_AR and GlyR mediated cross-talk in spinal cord and brain stem may precisely regulate the time course of the post-synaptic conductance during development. This may play an important role in motor coordination and the generation of locomotor patterns (Jonas et al., 1998; O'Brien and Berger, 1999), however this possibility so far has not been investigated. The interaction possibly also helps in shaping odor information processing in developing olfactory bulb (Trombley et al., 1999) and acoustic information processing in auditory synapses (Lu et al., 2008). Finally, it provides a mechanism that ensures efficient synaptic inhibition even in the case of a mutation in the one or the other transmitter receptor types.

CROSS-TALK OF GABA_A WITH NICOTINIC ACETYLCHOLINE RECEPTORS

Nicotinic acetylcholine receptors (nAChRs) are other major members of the cys-loop receptor family. In contrast to GABA_ARs, that are ligand-gated anion channels, nAChRs are ligand-gated cation channels. Co-localization of GABA and the ACh-synthesizing enzyme choline acetyltransferase has been demonstrated in rodent cortical neurons (Hallanger et al., 1986), chick retina amacrine-like cells (O'Malley and Masland, 1989; Santos et al., 1998) and in the nerve fibers innervating adrenal gland (Iwasa et al., 1999). Moreover, several studies have convincingly demonstrated that GABA can be co-released with ACh from cholinergic terminals (O'Malley and Masland, 1989; O'Malley et al., 1992; Lee et al., 2010). Unlike co-release of GABA and glycine, which involves release from the same vesicles, all these studies suggested the involvement of different vesicle pools in the co-release of GABA and ACh (Santos et al., 1998; Lee et al., 2010). Even though it is well established that GABA can be co-released at cholinergic nerve terminals, very few studies have focused on post-synaptic co-localization of GABA_A and nACh receptors. There is some evidence that the $\alpha 7$ -subtype containing nAChRs co-localize with GABA_ARs in interneurons of embryonic hippocampus (Kawai et al., 2002; Zago et al., 2006). It remains to be elucidated, however, if other subtypes of nAChRs apart from the $\alpha 7$ -subtype also co-localize with GABA_ARs in brain regions where GABA and acetylcholine are co-released.

Direct evidence of a post-synaptic cross-talk between GABA_ARs and $\alpha 7$ -nAChRs comes from recent studies on rodent hippocampal interneurons and on chick ciliary ganglion neurons (Wanaverbecq et al., 2007; Zhang and Berg, 2007). Using whole-cell voltage clamp recording, it was demonstrated that activation of post-synaptically localized $\alpha 7$ -nAChRs reversibly inhibited GABAergic inhibitory post-synaptic currents (IPSCs) by generating a calcium influx, resulting in Ca²⁺/calmodulin-dependent kinase II (CaMKII), Mitogen-activated protein kinase (MAPK; Zhang and Berg, 2007), and protein kinase C (PKC; Wanaverbecq et al., 2007) dependent phosphorylation of GABA_ARs. This inhibition was observed in autonomic neurons where $\alpha 7$ -nAChRs are concentrated on the soma along with GABA_ARs, and on hippocampal interneurons where $\alpha 7$ -nAChRs often co-cluster with GABA_ARs on dendrites and filopodia (Zhang and Berg, 2007). It however remains to be determined if Ca²⁺ influx via $\alpha 7$ -nAChRs may additionally result in phosphorylation and/or internalization of synaptic GABA_ARs. In any case, as hippocampal interneurons are spontaneously active by generating rhythms (Cobb et al., 1995) even when glutamatergic transmission is blocked, their regulation by $\alpha 7$ -nAChRs, which are highly enriched in interneurons, possibly plays an important role in modulating inhibitory neurotransmission.

In addition, pre-synaptic nAChRs depending on their subunit composition are known to facilitate action-potential dependent GABA release in hippocampal interneurons (Alkondon et al., 1997, 1999; Ji and Dani, 2000; Buhler and Dunwiddie, 2002), superficial superior colliculus neurons (Endo et al., 2005), and ventral tegmental area dopamine neurons (Yang et al., 2011). Surprisingly, Wanaverbecq et al. (2007), in their study, also observed an increase

in pre-synaptic GABA release along with post-synaptic suppression of GABA_AR-mediated IPSCs, effects that should oppose each other. In any case, cholinergic input can both facilitate as well as suppress GABAergic neurotransmission via complex pre-synaptic as well post-synaptic mechanisms. Further studies addressing regulation of GABA_ARs by both pre- and post-synaptic nAChRs are required to provide clues on the mechanism and function of this fine tuning.

CROSS-TALK OF GABA_A WITH SEROTONIN RECEPTORS

Serotonin (5-Hydroxytryptamine, 5-HT) is a monoamine transmitter that exerts its action by binding to serotonin receptors (5-HTRs) that are widely expressed in the nervous system as well as in non-neuronal tissue. Apart from the 5-HT₃R subtype, which is a ligand-gated ion channel and member of the *cys*-loop receptor family, all other serotonin receptors (5-HT_{1,2,4-7}) belong to the G-protein coupled receptor family (Hoyer et al., 2002; Kitson, 2007). So far, the only evidence for a co-localization of the transmitters GABA and serotonin comes from a recent study in the early vertebrate sea lamprey, where serotonin and GABA was demonstrated to co-exist in several brain regions (Barreiro-Iglesias et al., 2009a). Whether such a co-existence of these neurotransmitters and their receptors is also present in the mammalian nervous system, still needs to be determined. Furthermore, a co-release of serotonin with GABA (along with ATP) has only been reported in non-neuronal rat pancreatic beta cells (Braun et al., 2007), and thus, a possible co-release in the CNS still needs to be investigated.

However, a recent study for the first time described a cross-talk between 5-HT₃Rs and GABA_ARs in myenteric neurons using whole-cell recordings (Miranda-Morales et al., 2007), by providing evidence for current occlusion on simultaneous activation of these two receptors. The cross-talk as observed at saturating concentration of agonists for both receptors occurred immediately after the application of the two agonists, possibly suggesting that the two receptors are located very close to each other. The authors provided additional evidence for an allosteric interaction as they observed current occlusion even in the absence of Ca²⁺ and also in the presence of staurosporine, a general protein kinase inhibitor. Further experiments will have to investigate the mechanism of interaction of these receptors. As 5-HT₃R have a preferential localization on a sub-population of GABAergic interneurons in hippocampus and cortex, cross-talk between 5-HT₃Rs and GABA_ARs possibly may play a crucial role in the control of the balance between excitation and inhibition in the CNS (Chameau and van Hooft, 2006). It may also be important to note that the co-localization as reported for nACh/GABA_A and 5-HT₃/GABA_A receptors have been primarily observed in interneurons suggesting that nAChRs and 5-HT₃Rs possibly participate in fine tuning of inter-neuron functioning.

So far, there is no evidence of any post-synaptic cross-talk between GABA_ARs and G-protein coupled serotonin receptors. However, pre-synaptic potentiation of GABA release by serotonin, as well as by 5-HT₂ and 5-HT₃ receptors has been documented in spinal cord (Xu et al., 1998; Li et al., 2000; Fukushima et al., 2009) and hippocampal neurons (Dorostkar and Boehm, 2007). Whether these receptors additionally cross-talk with GABA_ARs receptors post-synaptically, still remains to be clarified.

CROSS-TALK OF GABA_A WITH DOPAMINE RECEPTORS

Dopamine receptors are G-protein coupled receptors consisting of five different subtypes, namely D1–D5 receptors. These receptors act via adenylyl cyclase mediated second messenger systems and are thus responsible for long-term regulation of brain functioning (Girault and Greengard, 2004). Even though there are only very few dopaminergic neurons, they have been described to actively regulate post-synaptic GABAergic signaling. Virtually all dopaminergic pre-synaptic terminals in glomerulus were reported to be glutamic acid decarboxylase (GAD) positive (Gall et al., 1987), suggesting a possible co-existence and co-release of the transmitters dopamine and GABA. This conclusion was supported by demonstrating co-localization of tyrosine hydroxylase and GAD in periglomerular cells in mouse brain slices (Maher and Westbrook, 2008). Additional evidence for the co-existence of dopamine and GABA came from a study on the brain of early vertebrate sea lamprey, where these two neurotransmitters were observed to co-exist in several brain regions (Barreiro-Iglesias et al., 2009b). Finally, Maher and Westbrook, in their study also reported the co-release of GABA and dopamine from dopaminergic nerve terminals of periglomerular cells.

Several studies have demonstrated that most, if not all members of the dopamine receptor family modulate post-synaptic GABA_AR-mediated neurotransmission in different regions of the brain. However, so far only dopamine D5 receptors have been demonstrated to directly bind to and cross-talk with GABA_ARs (Liu et al., 2000). It was demonstrated that D5, but not D1 receptor antibodies precipitated hippocampal GABA_ARs, indicating complex formation between these two receptors *in vivo*. Additionally, it was shown that the C-terminus of dopamine D5, but not D1 receptors could directly interact with the intracellular loop between the third and fourth transmembrane domain of the γ 2-subunit of GABA_ARs. In addition, the authors reported that co-activation of GABA_A and D5 receptors suppressed dopamine induced cAMP accumulation and resulted in current occlusion through GABA_ARs. In agreement with the absence of co-precipitation with D1 receptors, the authors observed no functional cross-talk. Actually, this was one of the first studies demonstrating that cross-talk could indeed occur via direct coupling between two receptors; however an additional involvement of adenylyl cyclase induced intracellular signaling following the activation of D1 receptors cannot be ruled out. Surprisingly, most of the other studies investigating dopamine/GABA_A receptor interaction only dealt with this second possibility.

Although Liu et al. (2000), observed no interaction and cross-talk of GABA_AR with D1 receptors in hippocampus, three other studies using whole-cell patch-clamp recordings, reported a suppression of GABA_AR-mediated chloride influx following activation of dopamine D1 receptors in olfactory bulb neurons (Brüning et al., 1999) and in the striatum (Flores-Hernandez et al., 2000; Goffin et al., 2010). Using radiolabeling and immunoprecipitation experiments, it was initially demonstrated that activation of D1 receptors increased the phosphorylation of β 1/ β 3 subunit of GABA_ARs via PKA/DARPP-32/PP1 (protein kinase A/Dopamine- and cAMP-regulated phosphoprotein/Protein phosphatase 1) signaling cascade, which in turn leads to reduced GABA-evoked currents in neostriatal medium spiny neurons (Flores-Hernandez

et al., 2000). Recently, Goffin et al. (2010) additionally showed that 10 min to 7 days treatment of striatal neurons with D1 receptor agonist resulted in a decreased number of GABA_ARs at the cell surface, eventually leading to a reduction in the number of GABAergic synapses and in GABA_AR cluster size. Surprisingly, they observed that the reduction in number of GABA_ARs was due to endocytosis followed by dephosphorylation of β -subunits by a protein phosphatase 2A-dependent pathway (PP2A; Goffin et al., 2010). Thus it seems likely, that the activation of D1 receptors results in rapid PKA-dependent phosphorylation of GABA_ARs, which over time, gets dephosphorylated by PP2A and eventually endocytosed, leading to sustained inhibition. The effect of GABA_AR activation on D1 receptor signaling and whether there is a direct interaction between the two receptors in striatal neurons was not investigated in these studies.

In similar lines, Goffin et al. (2010), additionally observed a D2 receptor-mediated down-regulation of surface GABA_ARs following dephosphorylation of β -subunits involving protein phosphatase 1 dependent pathway, eventually resulting in a smaller inhibitory response in the medium spiny neurons of the striatum (Goffin et al., 2010). In contrast, Brünig et al. (1999), had previously reported that D2 receptor activation resulted in an enhancement of GABAergic transmission due to a phosphorylation of GABA_ARs involving the protein kinase C pathway in mitral/tufted cells in the olfactory bulb. These discrepancies may possibly suggest a cell-type-specific modulation by dopamine receptors. More studies in this direction have to be performed to clarify this discrepancy. The reciprocal suppression of D2 receptor function by activation of GABA_ARs has been demonstrated in another study using dopamine D2 receptor radio-ligand binding assays in membrane preparation from rat neostriatum. It was demonstrated that the activation of GABA_ARs significantly increased the dissociation constant of the high affinity selective D2 receptor antagonist, raclopride, (Pérez de la Mora et al., 1997) which could be reversed by use of the GABA_AR antagonist bicuculline. Altogether, these results suggest a high probability of reciprocal cross-talk and possibly direct interaction between GABA_A/D2 receptors in similar lines as proposed for GABA_A/D5 receptors. However, this needs to be investigated further.

Finally, using whole-cell patch-clamp recordings in various brain regions, the last two members of the dopamine receptor family, the D3 and D4 receptors, have also been demonstrated to reduce GABAergic inhibition by stimulating endocytosis of GABA_ARs via the PKA/protein phosphatase I pathway. D3 receptors seem to reduce GABA_AR-mediated current by inactivating PKA activity, resulting in dephosphorylation of β -subunits, followed by clathrin/activator protein 2-mediated endocytosis of GABA_ARs in the nucleus accumbens (Chen et al., 2006) and hippocampus (Swant et al., 2008). Similarly, PKA/protein phosphatase I pathway-dependent rundown of GABA_ARs by D4 receptors has been reported in prefrontal cortex (Wang et al., 2002) and globus pallidus neurons (Shin et al., 2003). Functional experiments on dopamine receptors will clarify whether D3 or D4 receptors are also reciprocally inhibited followed by GABA_AR activation.

Based on all these studies, it seems clear that complex intracellular signaling pathways can be activated by dopamine receptors, which then determines the fate of nearby localized GABA_ARs.

In addition, a direct coupling and a reciprocal cross-talk between dopamine and GABA_A receptors cannot be ruled out. In any case, it seems that dopamine receptors are important regulators of surface GABA_AR expression. As GABA_ARs are highly mobile and continuously exchange between synaptic and extrasynaptic sites as well as by exocytosis and endocytosis, it is apparent that interactions with dopamine receptors may be one of the determinants for such rapid transition and therefore directly defining the strength of inhibitory synapse. Loss of coordination between the GABAergic and dopaminergic system could contribute to psychomotor and neuropsychiatric diseases in striatum and cortex, which affects both these pathways (Liu et al., 2000). Inhibition of GABA_AR-mediated IPSCs by dopamine receptors could enhance oscillations between globus pallidus neurons and subthalamic nucleus, thereby ameliorating Parkinson's disease (Shin et al., 2003). Additionally the action of dopamine on GABAergic inhibitory circuit in olfactory bulb could assist in odor detection and olfactory learning (Brünig et al., 1999).

CROSS-TALK OF GABA_A WITH P2X RECEPTORS

P2X receptors (P2XRs) are ligand-gated ion channels that are activated by adenosine-5'-triphosphate (ATP). Seven different subtypes of these receptors are now known (P2X₁–P2X₇) which assemble to form predominantly homo-trimeric but also heterotrimeric receptors (Burnstock, 2006). Even though ATP got late recognition as a neurotransmitter, it is now well established that it acts as a fast excitatory neurotransmitter and co-transmitter in several regions of the CNS. Synaptic co-release of ATP with GABA but not glutamate has been demonstrated in the rat spinal cord and mouse lateral hypothalamus (Jo and Schlichter, 1999; Jo and Role, 2002). Moreover, co-localization studies have clearly demonstrated the co-existence of P2X₂R-subtype with GABA_ARs in dorsal root ganglion (Labrakakis et al., 2003) and spinal cord neurons (Shrivastava et al., 2011), suggesting a possible physical association between these receptors.

A direct cross-talk between GABA_ARs and P2XRs was first demonstrated using whole-cell patch-clamp recording in rat dorsal root ganglion cells. It was demonstrated that co-application of the agonists of GABA_ARs and P2XRs produced a total current much smaller than the predicted linear summation of individual responses (Sokolova et al., 2001). This interaction was shown to be dependent on Ca²⁺ influx through endogenous P2XRs expressed in dorsal root ganglion neurons. Another study, investigated the mechanism of this cross-inhibition in more detail in a recombinant system after the co-expression of GABA_ARs and P2X₂Rs in *Xenopus* oocytes (Boué-Grabot et al., 2004b). Surprisingly, the authors observed the cross-talk to be independent of Ca²⁺ influx via P2X₂Rs. Additionally, they demonstrated that the intracellular C-terminus of P2X₂Rs and of the intracellular loop (between transmembrane domain III and IV) of GABA_AR β -subunit is essential for the interaction, which was additionally verified in our recent study (Shrivastava et al., 2011). In agreement with the previous study, Ca²⁺-independent cross-talk was also reported in myenteric neurons (Karanjia et al., 2006). Finally, a similar cross-talk between P2X₃Rs/GABA_ARs and P2X₄Rs/GABA_ARs was reported recently (Toulmé et al., 2007; Jo et al., 2011).

We studied this interaction in more detail by employing co-immunoprecipitation and FRET imaging in transiently transfected HEK cells, in combination with single particle tracking and quantitative immunocytochemistry in primary neurons of spinal cord. We demonstrated that GABA_ARs and P2X₂Rs interact with each other already intracellularly possibly within the endoplasmic reticulum and are then co-transported to the cell membrane where they are primarily co-localized extrasynaptically in mice spinal cord neurons (Shrivastava et al., 2011). Additionally we observed that upon activation of P2X₂Rs by ATP or P2X₂R agonists, this transient complex gets dissociated. This agonist-induced dissociation seems to be both Ca²⁺ dependent and thus mediated via signaling mechanisms and Ca²⁺ independent and thus mediated via a conformational change. Although this cannot explain the cross-talk observed by electrophysiological studies due to the much longer time course used in our studies, it appears that following activation of one of the two receptors, an initial Ca²⁺-independent (Boué-Grabot et al., 2004b; Karanjia et al., 2006) conformational change results in current occlusion, followed by a Ca²⁺-dependent (Sokolova et al., 2001; Shrivastava et al., 2011) dissociation of this receptor–receptor complex. Whether this Ca²⁺-influx additionally leads to activation of Ca²⁺-dependent intracellular signaling pathways, as reported for nACh and dopamine receptors, remains a highly intriguing question to be answered.

The importance of cross-talk involving members of P2XR family can be estimated by the fact that P2XRs not only cross-talk with GABA_ARs, but are now known to also cross-talk with most of the other members of cys-loop receptor family, possibly in a similar way (Zhou and Galligan, 1998; Khakh et al., 2000, 2005; Sokolova et al., 2001; Boué-Grabot et al., 2004a, 2004b; Karanjia et al., 2006; Decker and Galligan, 2009). P2XR-mediated regulation of GABA_AR number at the cell surface can have direct implications on modulating pain transmission in spinal cord (Zeilhofer et al., 2009; Shrivastava et al., 2011) or on epileptic seizures in hippocampus (Kang et al., 2003).

CROSS-TALK OF GABA_A WITH ADENOSINE RECEPTORS

Adenosine receptors are members of the G-protein coupled purine receptor family, with adenosine being their natural ligand. Four different adenosine receptors are known, namely A1, A2A, A2B, and A3 receptors (Burnstock, 2006). ATP released from pre-synaptic terminals rapidly degrades to ADP and adenosine by ectonucleotidases that are present in the synaptic cleft (Abbracchio et al., 2009). Thus, ATP co-released from GABAergic terminals (Jo and Schlichter, 1999) can also give rise to adenosine. An additional source of ATP and hence adenosine are astrocytes surrounding the neurons. Thus, it is highly probable that even in the absence of a direct co-release with GABA, adenosine may modulate GABA_AR signaling if adenosine receptors are in the vicinity of GABA_ARs. Although to the best of our knowledge no co-localization study of adenosine receptors and GABA_ARs has been published so far, there have been several reports suggesting a possible post-synaptic cross-talk of adenosine receptors and GABA_ARs.

Cross-talk between GABA_A and A1 receptors has been reported in dorsal root ganglion neurons and sacral dorsal commissural nucleus neurons where a suppression of post-synaptic GABA_AR-mediated chloride current was observed in the presence of

adenosine and the A1 receptor agonist N6-cyclohexyladenosine but not the A2A receptor agonist 2-[p-(2-carboxyethyl)-phenethylamino]-5'-N-ethylcarboxamidoadenosine (Hu and Li, 1997; Li et al., 2004) using voltage-clamped whole-cell patch recordings. The suppression effect of adenosine could be blocked specifically by the A1 receptor antagonist, 8-cyclopentyl-1,3-dipropylxanthine. Interestingly, this inhibition of GABA_AR-mediated chloride flux was observed to occur via a Ca²⁺-independent–PKC-dependent pathway and also did not involve PKA-dependent pathways. Although the involvement of PKC strongly suggests that post-synaptic A1 receptors were mediating this response, a possible inhibition of GABA release by pre-synaptic A1 receptors cannot be ruled out. Surprisingly, no study was published in the last few years investigating this cross-talk further. However, a couple of recent studies suggest an important functional role of adenosine receptors in the regulation of GABAergic transmission under pathological conditions. After injecting neurosurgically resected epileptic human brain tissue in *Xenopus* oocytes, the oocytes use the mRNAs present in the tissue to synthesize the respective proteins and receptors that then can be investigated electrophysiologically by whole-cell recordings. When GABA_ARs expressed by these oocytes were investigated, the authors observed a rundown of the GABA-induced current on repetitive application of GABA, which could be significantly reduced by antagonists of A2A, A2B, and A3 receptors and surprisingly not by those of A1 receptors. A similar effect was found in rodent brain (Roseti et al., 2008, 2009). The mechanism behind this effect remains to be elucidated, however the authors speculate on the possible involvement of MAPK and/or PKA-dependent pathway regulating the rundown of GABA_AR-mediated current. Adenosine receptor-mediated regulation of GABA_AR functioning has additionally been implicated in hypoxia, ischemia, and pain, which is supported by that fact that under the conditions of tissue injury and inflammation, an increase in the levels of purines in the neuronal system is observed (Gourine et al., 2007). It is highly interesting to speculate that a functional cross-talk between GABA_ARs and adenosine receptors may play an important role under conditions of neuro-inflammation.

CROSS-TALK OF GABA_A WITH N-METHYL-D-ASPARTATE RECEPTORS (NMDA) RECEPTORS

Several studies have demonstrated that glutamate and GABA can be co-released from inhibitory as well as excitatory nerve terminals. This is not surprising because glutamate is the precursor for the synthesis of GABA. In one of the first studies, the presence and release of glutamate and aspartate, in addition to GABA, was demonstrated from the anti-GAD immune-purified GABAergic synaptosomal preparations from brain cortex (Docherty et al., 1987). These GABAergic synaptosomes released glutamate in response to depolarizing treatments with either potassium or veratrine, a sodium channel activator. However, whether these synaptosomal preparations were in fact purely GABAergic and not contaminated with glutamatergic synaptosomes cannot be answered retrospectively. Recent studies have identified the type 3 vesicular glutamate transporter (VGLUT3) to be co-localized extensively with vesicular GABA transporter (VGAT) around unstained pyramidal cells and granule cells in the hippocampus

(Boulland et al., 2004) and in developing auditory medial nucleus of the trapezoid body (Gillespie et al., 2005). Boulland et al. (2004), additionally observed a dramatic increase in co-localization of VGAT and VGLUT3 in GABAergic nerve terminals during early stages of development suggesting co-release of glutamate along with GABA plays a crucial role during development. In fact, a very recent work demonstrated that the co-transmission of glutamate in developing GABA/glycinergic sound localization pathway is crucial for synaptic reorganization of inhibitory circuits and disruption of glutamate co-transmission prevented the strengthening of inhibitory connections that would normally occur with maturation (Noh et al., 2010). In a very recent study, Fattorini et al. (2009), observed that GABAergic synapses can express VGLUT1 and glutamatergic synapses can express VGAT. This was further supported by immunoisolation experiments demonstrating that anti-VGAT immunoisolated vesicles contained VGLUT1 and anti-VGLUT1 immunoisolated vesicles contained VGAT (Fattorini et al., 2009). A more recent work using postembedding immunogold double labeling additionally revealed that VGLUT1, VGLUT2, and VGAT coexist in mossy fiber terminals of the hippocampal CA3 area and cerebellar mossy fiber terminals. The presence of VGLUT2 was also demonstrated in cerebellar GABAergic basket cells in this study (Zander et al., 2010).

The co-localization of pre-synaptic transporters for co-released glutamate and GABA suggests a possible co-localization of their respective receptors at post-synaptic terminals. So far, co-localization of glutamate receptors at GABAergic synapses has not been extensively investigated. Recently, however, the existence of NMDA receptors in hippocampal CA1 and CA3c GABAergic synapses has been demonstrated (Szabadits et al., 2011). In these synapses NMDA receptors triggered a retrograde nitric oxide-cGMP cascade, thus modulating GABAergic inhibition in an activity-dependent manner. Since GABAergic inhibition plays a central role in the control of pyramidal cell ensemble activities, such a regulation is able to fine-tune network patterns.

In contrast, localization of GABA_ARs at the post-synaptic membrane of glutamatergic synapses has been demonstrated in several studies. Thus, using electron microscopic immunogold labeling, it was demonstrated that the $\alpha 6$, but not the $\alpha 1$ subunit of GABA_ARs was also concentrated in glutamatergic cerebral mossy fiber synapses (Nusser et al., 1996). More functional evidence on the existence of GABA_ARs at glutamatergic synapses comes from a very recent study where the authors observed that at puberty, expression of inhibitory $\alpha 4$ and δ subunits of GABA_ARs increased by 700% on the plasma membrane perisynaptically to asymmetric glutamatergic synapses of hippocampal CA1 pyramidal neurons (Shen et al., 2010). Among other subunits, the primarily extrasynaptically localized $\alpha 5$ subunit has also been detected at excitatory synapses (Crestani et al., 2002). The existence of post-synaptic GABA_ARs at excitatory synapses may serve to regulate the time course of excitation and to limit glutamatergic overexcitation and subsequent excitotoxicity.

Post-synaptically, glutamate exerts its action via ionotropic NMDARs, AMPARs, and kainate receptors, or metabotropic glutamate receptors (Dingledine et al., 1999). Among these, NMDA receptors have been best studied and shown to directly modulate GABA_AR functioning in a Ca²⁺ dependent manner. NMDA

receptors are highly permeable to Ca²⁺ and are localized to post-synaptic densities, where they are structurally organized in characteristic spines (Lau and Zukin, 2007). Several studies demonstrate that activation of NMDARs resulted in the suppression of GABA_AR function due to calcium dependent activation of phosphatase 2B/calcineurin and consecutive dephosphorylation of GABA_ARs in hippocampus (Stelzer and Shi, 1994; Chen and Wong, 1995; Marsden et al., 2007; Bannai et al., 2009) and cerebellum granule cells (Robello et al., 1997). Following dephosphorylation of serine-327 in the intracellular loop of GABA_ARs $\gamma 2$ -subunit, synaptic GABA_ARs then escape to extrasynaptic sites (Wang et al., 2003; Bannai et al., 2009; Muir et al., 2010). In contradiction to all these observations, one study reported that NMDAR activation resulted in the removal of AMPARs from the membrane while simultaneously increased expression of surface GABA_ARs (Marsden et al., 2007). However, this pathway was dependent on Ca²⁺/calmodulin-dependent protein kinase II (CaMKII). This discrepancy possibly could be explained on the basis of the Ca²⁺ level in the cell followed by activation of NMDARs. NMDAR activation of CaMKII is generally associated with high levels of Ca²⁺ influx (Silva et al., 1992), so depending on the level of Ca²⁺ influx through NMDARs, phosphatases (calcineurin), or kinases (CaMKII) may be activated resulting in a decrease or increase of surface GABA_ARs, respectively. Thus, it seems clear that glutamate primarily acting via NMDARs can modulate the expression of GABA_ARs, thus modulating inhibition. It would be interesting to see whether GABA acting via GABA_ARs can also modulate NMDAR expression or function. However a direct cross-talk of NMDARs and GABA_ARs has not been investigated in these studies.

CONCLUSION

Recently it was demonstrated that several members of the G-protein coupled receptors can heteromerize, thus producing functional entities that possess different biochemical characteristics with respect to the individual components of the heteromer. In addition, the qualitative or quantitative aspects of the signaling generated by stimulation of any of the individual receptor units in the heteromer are different from those obtained during co-activation, they thus exhibit "cross-talk" (Ferré et al., 2007). A similar heteromerization obviously can also occur between different types of ligand-gated ion channels and ligand-gated ion channels and G-protein coupled receptors. These interactions allow cross-talk between different signaling pathways, but to date, their molecular nature and functional implications are poorly understood. Here we provide an overview on the current knowledge on the interactions of GABA_AR with other ligand-gated ion channels or metabotropic G-protein coupled receptors at the post-synaptic membrane.

GABA_ARs have been clearly demonstrated to heteromerize with GABA_BRs (Balasubramanian et al., 2004), dopamine D5 receptors (Liu et al., 2000), and purinergic P2XRs (Jo et al., 2011; Shrivastava et al., 2011). All these receptors have also been demonstrated to cross-talk with GABA_ARs, resulting in a decrease in GABAergic neurotransmission. As other members of the dopamine receptor family are also known to cross-talk with GABA_ARs, other dopamine receptors (D1–D4) may

also heteromerize with GABA_ARs. Additional experiments will have to be performed to investigate this possibility. Although there is strong evidence of a functional interaction and colocalization of GABA_ARs and GlyRs, a direct coupling between them so far has not been demonstrated. In cross-talk studies involving serotonin 5-HT₃Rs, the authors proposed a very close proximity with GABA_ARs, as they observed current occlusion even in the absence of Ca²⁺ or protein kinase inhibitor. As the cross-talk reported was similar to the one described for GABA_A/P2X receptors, a possible direct coupling remains a challenging issue to be addressed. Among other receptors known to cross-talk with GABA_ARs are nAChRs and adenosine receptors. However, so far evidence is too weak to speculate on a direct interaction of these receptors with GABA_ARs. Lastly, NMDAR mediated down-regulation of GABA_ARs and thus disinhibition of the respective neuron possibly involves only intracellular signaling mechanisms.

Whereas heteromerization of GABA_AR with other receptors in most cases has been demonstrated at synapses, such interactions may also occur at extrasynaptic sites, as observed for GABA_A/P2X₂ receptor interactions regulating tonic inhibition. In addition, it was demonstrated that these receptors already interact with each other in intracellular compartments, possibly providing a mechanism of specifically targeting the heteromer to extrasynaptic sites. A similar intracellular interaction followed by co-trafficking to the cell membrane has also been observed for GABA_AR and GABA_BRs (Balasubramanian et al., 2004). Similar studies have not been performed so far with other receptors that heteromerize with GABA_ARs.

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