$GABA_B$ Receptor Chemistry and Pharmacology: Agonists, Antagonists, and Allosteric Modulators

A. Nieto, T. Bailey, K. Kaczanowska, and P. McDonald

Contents

Abstract The $GABA_B$ receptors are metabotropic G protein-coupled receptors (GPCRs) that mediate the actions of the primary inhibitory neurotransmitter, γ-aminobutyric acid (GABA). In the CNS, GABA plays an important role in behavior, learning and memory, cognition, and stress. GABA is also located throughout the gastrointestinal (GI) tract and is involved in the autonomic control of the intestine and esophageal reflex. Consequently, dysregulated $GABA_B$ receptor signaling is associated with neurological, mental health, and gastrointestinal disorders; hence, these receptors have been identified as key therapeutic targets and are the focus of multiple drug discovery efforts for indications such as muscle spasticity

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disorders, schizophrenia, pain, addiction, and gastroesophageal reflex disease (GERD). Numerous agonists, antagonists, and allosteric modulators of the $GABA_B$ receptor have been described; however, Lioresal® (Baclofen; β-(4-chlorophenyl)-γ-aminobutyric acid) is the only FDA-approved drug that selectively targets $GABA_B$ receptors in clinical use; undesirable side effects, such as sedation, muscle weakness, fatigue, cognitive deficits, seizures, tolerance and potential for abuse, limit their therapeutic use. Here, we review $GABA_B$ receptor chemistry and pharmacology, presenting orthosteric agonists, antagonists, and positive and negative allosteric modulators, and highlight the therapeutic potential of targeting $GABA_B$ receptor modulation for the treatment of various CNS and peripheral disorders.

Keywords $GABA_B$ receptor pharmacology · Orthosteric and allosteric modulators · Therapeutic target

1 Introduction

γ-aminobutyric acid (GABA) is one of the most widely distributed amino acid neurotransmitters in the central nervous system (CNS), acting as the primary neurotransmitter responsible for neuronal inhibition. GABA activities are mediated through two distinct classes of receptors; ionotropic $GABA_A$ and $GABA_A$-ρ (formerly known as $GABA_C$, and prominently expressed in the retina (Naffaa et al. 2017)) and metabotropic $GABA_B$ receptors (Bowery et al. 2004). $GABA_A$ and $GABA_A$-ρ ionotropic receptor subunits form ion channels that are selectively permeable to anions like chloride and are responsible for the transient and rapid component of inhibitory postsynaptic potentials (Sigel and Steinmann 2012). Whereas, the metabotropic $GABA_B$ receptors belong to the superfamily of G-protein-coupled receptors (GPCRs) and mediate the slow and prolonged component of synaptic inhibition via indirect gating of neuronal K^+ and Ca^{2+} channels and lowering levels of other second messenger targets like cAMP (Bowery et al. 2002).

$GABA_B$ receptors are broadly expressed and distributed in the CNS. They are located pre- and postsynaptically; activation of presynaptic $GABA_B$ receptors by GABA located on GABAergic terminals (autoreceptors) inhibits the release of GABA, while activation of presynaptic $GABA_B$ receptors located on other nerve terminals (heteroreceptors) inhibits the release of several other neurotransmitters such as glutamate and bioactive peptides. In contrast, activation of postsynaptic receptors activate K^+ channels and induce slow inhibitory postsynaptic potentials (Benarroch 2012). $GABA_B$ receptors are also located in the periphery along the gastrointestinal (GI) tract where they regulate intestinal motility, gastric emptying, gastric acid secretion, and esophageal sphincter relaxation (Clarke et al. 2018; Lehmann et al. 2010; Ong and Kerr 1984). Dysregulated $GABA_B$ receptor function has been implicated in a variety of neurodegenerative diseases and

pathophysiological disorders, including Parkinson's disease (Nambu 2012; Tyagi et al. 2015), Alzheimer's disease (Rice et al. 2019; Sun et al. 2020), Huntington's disease (Kim and Seo 2014), epilepsy (Billinton et al. 2001a; Teichgräber et al. 2009), spasticity (Francisco et al. 2001; Basmajian 1975; Korsgaard 1976), pain (Neto et al. 2006; Enna and McCarson 2006; Murai et al. 2019), anxiety (Kalinichev et al. 2017; Li et al. 2015) and depression (Cryan and Kaupmann 2005; Felice et al. 2012; Jacobson et al. 2018), schizophrenia (Glausier and Lewis 2017; Nair et al. 2020), narcolepsy (Black et al. 2014; Szabadi 2015), and addiction (Agabio and Colombo 2014, 2015; Agabio et al. 2018; Maccioni and Colombo 2019; Ranson et al. 2020). Owing to their presence in the gastrointestinal tract these receptors are also implicated in a variety of GI disorders such as gastroesophageal reflux disease (GERD) (Clarke et al. 2018; Lehmann et al. 2010; Ong and Kerr 1984; Lehmann 2009; Symonds et al. 2003).

2 Brief History

While GABA was discovered in the mammalian brain in 1950 (Awapara 1950; Roberts and Frankel 1950), it was not recognized as an inhibitory neurotransmitter until 1967 (Krnjević and Schwartz 1966; Dreifuss et al. 1969). Early attempts to interrogate the GABA system led to the development of the synthetic agonist, β-(4-chlorophenyl)-γ-aminobutyric acid, a poorly brain penetrant derivative of GABA better known as baclofen (Keberle et al. 1969). In 1968 the identification of the first GABA receptor antagonist "bicuculline" was reported (Curtis et al. 1970), and in 1987, bicuculline and GABA receptor agonists such as isoguvacine facilitated the cloning of the ionotropic $GABA_A$ receptor, a pentameric ligand gated ion channel (Schofield et al. 1987).

The existence of the $GABA_B$ receptors (so named to distinguish it from the $GABA_A$ receptor) first emerged in 1979. Dr. Norman Bowery and colleagues discovered that GABA blocks the release of neurotransmitters such as norepinephrine from nerve terminals but this effect was not blocked by bicuculline, instead it mimicked the effects of baclofen. It was also discovered that baclofen does not interact with the $GABA_A$ site (Bowery et al. 1979, 1980, 1981). A third GABA receptor with pharmacology distinct from $GABA_A$ and $GABA_B$ was identified in 1986 by virtue of the GABA response, "Cl-current blocked by picrotoxin," being both bicuculline and baclofen insensitive (Johnston 1986). This receptor was named $GABA_C$ (now referred to as $GABA_A$-ρ) and was later cloned in 1991 (Polenzani et al. 1991). However, it was almost 20 years since being identified that the $GABA_B$ receptor was cloned using expression cloning and radioligand binding of a high affinity antagonist (1997) by the Bettler group (Kaupmann et al. 1997). Thus, reagents that modulate the GABA receptors facilitated the cloning of, and have since defined those receptors; the ionotropic receptors $GABA_A$ and $GABA_A$-ρ are defined as "bicuculline-sensitive, isoguvacine-sensitive" and

"bicuculline-insensitive, baclofen-insensitive" respectively, and the metabotropic $GABA_B$ receptor is defined as "bicuculline-insensitive, baclofen-sensitive."

3 Structure and Signaling

In common with other GPCRs, the $GABA_B$ receptor is an integral membrane protein that spans the cellular membrane with seven helices that are linked by three extracellular loops and three intracellular loops and possesses an extracellular N-terminus and an intracellular C-terminus. $GABA_B$ receptors are structurally related to metabotropic glutamate receptors (mGluRs), and together with the calcium-sensing receptor (CaSR), some pheromone and taste receptors, and orphan GPCRs (receptors with no known ligands), belong to the family C (or family III) of GPCRs (Bowery et al. 2002). Common to the members of family C GPCRs is the large extracellular N-terminus that contains a domain homologous to the periplasmic amino acid binding proteins (PBPs) found in bacteria. The X-ray structure of $GABA_B$ receptor PBP-like domains revealed an orthosteric ligand binding pocket that is made up of two globular lobes separated by a hinge region. The two lobes (LB1 and LB2) close upon ligand binding, much like a Venus flytrap does when touched by an insect, hence the globular domains in family C GPCRs are also referred to as "Venus flytrap" (VFT) domains (Galvez et al. 1999); an agonist binds and stabilizes the closed (active) conformation of the VFT, whereas an antagonist stabilizes and retains the VFT subunit in the open (inactive) configuration.

To date molecular cloning has identified two main $GABA_B$ receptor subunits, namely $GABA_{B1}$ and $GABA_{B2}$ which arise from distinct genes (Kaupmann et al. 1997, 1998). At the protein level $GABA_{B1}$ and $GABA_{B2}$ receptors share 35% identity and 54% similarity over their approximate length of 950 amino acid residues and both subunits are highly conserved across mammalian species, sharing 90–95% sequence homology between human, pig, rat, and mouse (Kaupmann et al. 1997). An active functional $GABA_B$ receptor with high affinity for agonist ligands depends upon the formation of a heterodimer between $GABA_{B1}$ and $GABA_{B2}$ receptor subunits (Kaupmann et al. 1998; Marshall et al. 1999; Jones et al. 1998). The association of the receptor subunits occurs, at least in part, through a coiled-coil motif found in the respective carboxyl termini of $GABA_{B1}$ and $GABA_{B2}$ subunits. It has been demonstrated in recombinant systems that $GABA_{B1}$ is unable to reach the cell surface in the absence of the $GABA_{B2}$ subunit because $GABA_{B1}$ contains endoplasmic retention motifs in its carboxy tail that are masked only upon heterodimerization with $GABA_{B2}$ subunit (Couve et al. 1998; Pagano et al. 2001). Interestingly, all orthosteric agonists and antagonists bind to the $GABA_{B1}$VFT and not to the $GABA_{B2}$ subunit VFT. Upon binding, an agonist induces conformational changes in the $GABA_{B1}$ subunit which by virtue of its physical interaction with the $GABA_{B2}$ subunit promotes conformational changes in the latter subunit allowing it to couple to its cognate G-protein promoting functional responses within the cell

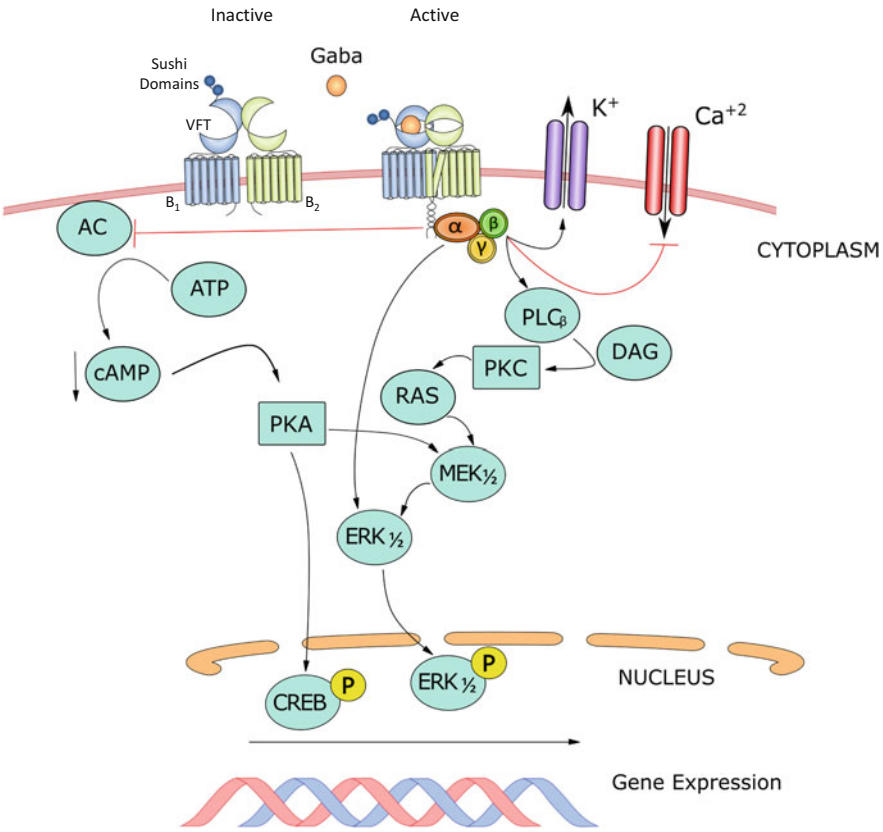


Fig. 1 Molecular diversity and signaling capacity of the GABA$_B$ receptor

(Galvez et al. 2001; Margeta-Mitrovic et al. 2001; Robbins et al. 2001; Duthey et al. 2002).

GABA$_B$ receptors provide a crucial component of inhibitory neurotransmission mainly via coupling to heterotrimeric $G_{i/o}$ type G-proteins, activation of which results in a Gα-mediated inhibition of cAMP production and a Gβγ-mediated modulation of the activity of ion channels such as high voltage-activated Ca^{2+} (Ca_v) channels and G protein-coupled inwardly rectifying Kir3-type potassium channels (GIRKs) (Morishita et al. 1990; Nishikawa et al. 1997). In rare cases and non-neuronal cells, GABA$_B$ receptor activation can promote increases in intracellular calcium either via activation of phospholipase C and store-operated channels or by inducing Ca^{2+} release from internal stores (Meier et al. 2008; New et al. 2006). Furthermore, GABA$_B$ receptor activation has been reported to induce phosphorylation of the Extracellular-signal Regulated protein Kinase 1/2 ($ERK_{1/2}$) in cerebellar neurons, as well as in the CA1 field of the mouse hippocampus (Tu et al. 2007; Vanhoose et al. 2002). Thus, GABA$_B$ receptor couples to multiple intracellular signal transduction pathways (Fig. 1) regulating ion homeostasis as well as MAPK

signaling leading to downstream effects that include blocked neurotransmitter release and hyperpolarization of neurons (Bowery et al. 2002; Bettler et al. 2004), and the modulation of autonomic control of the intestine and esophageal reflex (Clarke et al. 2018; Ong and Kerr 1984; Lehmann 2009; Symonds et al. 2003).

4 Molecular Diversity and Complexity

Molecular diversity in the $GABA_B$ receptor system arises from expression of multiple $GABA_{B1}$ subunit isoforms of which 14 mammalian isoforms ($GABA_{B(1a\text{-}1n)}$) exist between various animal species and are generated by differential transcription or splicing (Bettler et al. 2004), whereas the $GABA_{B2}$ receptor encodes a singular form of the receptor (Bettler et al. 2004; Billinton et al. 2001b). The two predominant $GABA_{B1}$ isoforms, termed $GABA_{B(1a)}$ and $GABA_{B(1b)}$, are generated by use of alternative transcription start sites, whereas other less abundant isoforms such as $GABA_{B(1c)}$, and $GABA_{B(1e)}$ are generated by alternative splicing. Only the $GABA_{B(1a)}$ and $GABA_{B(1b)}$ variants have been identified as components of the native receptor $GABA_{B1}$/$GABA_{B2}$ complex. Although the identification of these variants is suggestive of pharmacologically distinct $GABA_B$ receptors, Ng and colleagues reported that the anticonvulsant gabapentin acts as an agonist at $GABA_{B(1a)}$ but not $GABA_{B(1b)}$ (Bertrand et al. 2001; Ng et al. 2001), this has been widely disputed as heterodimers comprised of either $GABA_{B(1a)}$/$GABA_{B2}$ or $GABA_{B(1b)}$/$GABA_{B2}$ are pharmacologically indistinguishable in heterologous systems (Jensen et al. 2002; Lanneau et al. 2001) and to date, no $GABA_B$ receptor ligand differentiates between these molecular variants. However, studies facilitated by the generation of $GABA_{B1}$ isoform-specific knockout mice (Vigot et al. 2006) demonstrated that $GABA_{B1a}$- and $GABA_{B1b}$-containing receptors have distinct functions owing to their different locations within neurons, where $GABA_{B1a}$ receptors are predominantly located presynaptically on axonal terminals and $GABA_{B1b}$ postsynaptically on dendritic spines. Consequently, global $GABA_{B1}$ receptor isoform knockout mice exhibit a wide spectrum of isoform-specific behaviors. For example, using the isoform-specific knockout mice, Vigot et al. showed that $GABA_{B1a}$ and not $GABA_{B1b}$ receptor was involved in impaired synaptic plasticity in hippocampus long-term potentiation (Vigot et al. 2006). It was also shown by Perez-Garci and colleagues that $GABA_{B1b}$ was responsible for mediating postsynaptic inhibition of Ca^{2+} spikes, whereas presynaptic inhibition of GABA release was mediated by $GABA_{B1a}$ (Pérez-Garci et al. 2006). Hence, based on numerous in vivo findings, the existence of pharmacologically distinct $GABA_B$ receptors has been proposed (Pinard et al. 2010).

$GABA_{B(1a)}$ and $GABA_{B(1b)}$ differ primarily in their extracellular amino-terminal domains by a pair of sushi domains only present in the $GABA_{B(1a)}$ subunit of the $GABA_{B1(a)}$/$GABA_{B2}$ heteromer (Bettler et al. 2004; Hawrot et al. 1998). Sushi domains, or short consensus repeats, are conserved protein domains commonly involved in protein–protein interactions mostly found in proteins involved in cell–

cell adhesion. In the context of the $GABA_B$ receptor, the sushi domains have been shown to play a role in targeting the $GABA_{B(1a)}$ receptor to specific subcellular regions by means of interaction of these motifs with proteins in the extracellular matrix or on the surface of neighboring cells (Hannan et al. 2012). The diversity in $GABA_{B1}$ isoforms may therefore provide a means for targeted subcellular localization and/or coupling to distinct intracellular signaling pathways while also providing, in part, an explanation for the complex and diverse physiology effects of the GABA/$GABA_B$ receptor axis observed in neuronal tissue and in vivo (Bettler and Tiao 2006).

The molecular complexity of the $GABA_B$ receptor is further enhanced through association of the receptor with numerous trafficking, effector, and regulatory proteins, as well as other membrane-bound receptors. For example, the extracellular matrix protein, fibulin-2, has been shown to bind to the first sushi domain of the $GABA_{B(1a)}$ and target this receptor to axon terminals of excitatory synapses (Blein et al. 2004). Likewise, amyloid precursor protein (APP), amyloid precursor protein-like 2 (APLP2), and adherence junction associated protein-1 (AJAP1) interact with the sushi domains and are also anticipated to direct axonal subcellular localization of the $GABA_{B(1a)}$/$GABA_{B2}$ receptor complex (Dinamarca et al. 2019). Whereas $GABA_{B(1b)}$-containing heteromers more frequently show dendritic localization (Vigot et al. 2006).

Furthermore, a subfamily of the potassium channel tetramerization domain (KCTD) proteins (KCTD 8, 12, 12b, and 16) has been shown to exclusively and constitutively interact with the $GABA_{B2}$ carboxy-terminus acting as auxiliary subunits of the receptor to regulate the kinetics and outcome of G-protein signaling (Bartoi et al. 2010; Schwenk et al. 2010). For example, the KCTD12 and 12b subunits mediate desensitization of the receptor, whereas KCTD8 and 16 regulate non-desensitizing activities. The receptor, KCTD subunits, and G-protein combined form the core receptor signaling complex required for normal function of inhibitory brain circuits. Recently, Zuo et al., reported a high-resolution crystal structure of the KCTD16 oligomerization domain in complex with a $GABA_{B2}$ C-terminal peptide and together with mutational analysis defined the interface between KCTD16 and $GABA_{B2}$ revealing a potential regulatory site that modulates $GABA_B$ receptor activity (Zuo et al. 2019).

Other proteins have been reported to transiently associate with the $GABA_B$ receptor either directly through $GABA_{B1}$ or $GABA_{B2}$ carboxy terminal domains, which include transcription factors (i.e., ATF-4 (CREB2) and CHOP (Gadd153) (Nehring et al. 2000; Ritter et al. 2004; Sauter et al. 2005)) and scaffolding and adaptor proteins (i.e., MUPP1, 14-3-3 protein, and NSF (Balasubramanian et al. 2007; Couve et al. 2001; Pontier et al. 2006)) or indirectly through multiprotein complexes, which include neuroligin-3, synaptotagmin-11, and calnexin (Schwenk et al. 2016). Novel functions of the $GABA_B$ receptor also arise through crosstalk with other membrane receptors such as $GABA_A$, mGluR1, NMDA, IGF-1, and TrkB receptors. For a more comprehensive description of the $GABA_B$ receptor interactome, see (Benke 2013; Fritzius and Bettler 2020).

Recent biophysical and structural studies have demonstrated that $GABA_B$ receptors can form higher-order multimeric receptor complexes and this has been shown to occur in both heterologous systems and in brain membranes. These multimers comprise oligomers of $GABA_{B1}$ and $GABA_{B2}$ heteromers that self-assemble through association of their $GABA_{B1}$ subunits into tetramers (dimers of dimers) and octamers (dimers of tetramers) (Comps-Agrar et al. 2011, 2012; Maurel et al. 2008). Tetramers were found to decrease $G\alpha_i$-protein coupling efficiency suggesting that the multimers exhibit negative cooperativity between heterodimers (Calebiro et al. 2013; Stewart et al. 2018). It has emerged that the core $GABA_{B1/B2}$ receptor not only assembles with itself (oligomerization) but can also form supercomplexes with other multiprotein complexes that are likely spatiotemporally regulated in response to neuronal and developmental cues (Fritzius and Bettler 2020). The role of higher-order receptor complexes in $GABA_B$ receptor function and physiology requires further investigation to determine the functional relevance of $GABA_B$ receptor oligomerization in native tissue.

5 Agonists

As mentioned previously, the synthesis of the GABA analogue baclofen (-β-(4-chlorophenyl)-GABA; Fig. 2) in 1962 as the prototypical $GABA_B$ receptor agonist (Keberle et al. 1964) has greatly facilitated the molecular and biochemical characterization of this receptor. Indeed, baclofen has served as an invaluable tool in elucidating the electrophysiological and behavioral responses linked to the $GABA_B$ receptor system revealing its versatility as a drug target to treat a wide variety of diseases (Bowery 1993; Froestl et al. 1995a, b). Owing to its extensive therapeutic potential, numerous attempts to improve baclofen's pharmacokinetic properties and

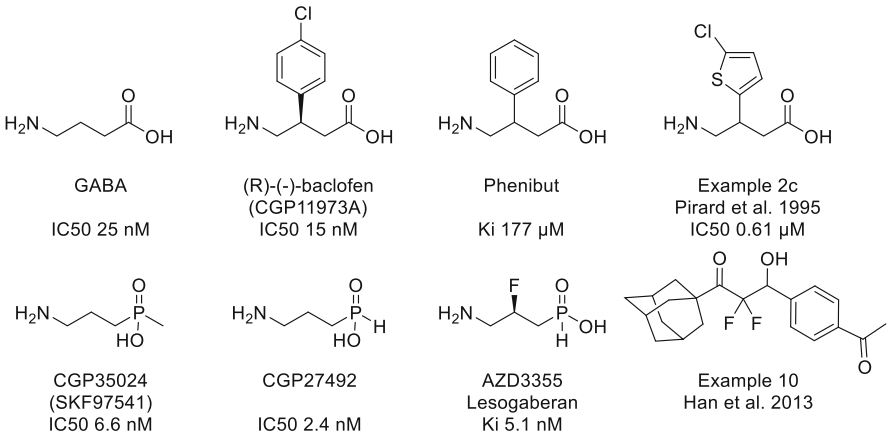


Fig. 2 Exemplar chemical structures of $GABA_B$ receptor full agonists

potency while maintaining selectivity have been pursued, but flat structure-activity relationships (SAR) around baclofen have resulted in very limited success. Of the 217 $GABA_B$ receptor-associated molecules reported in ChemBL Database (CHEMBL n.d.; Mendez et al. 2019), 55 compounds (42 agonists and 13 antagonists) are identified as being active at the $GABA_B$ receptor, most of which are chemically classified as analogues of either GABA or baclofen. However, the SAR investigations and the pharmacological properties of the resulting baclofen analogues have revealed important information regarding the chemical characteristics that endow baclofen with its activity at the $GABA_B$ receptor.

Following the resolution of baclofen in 1978 into the two enantiomers, (R)-(−)-baclofen and (S)-(+)-baclofen (Olpe et al. 1978; Weatherby et al. 1984) (CGP11973A and CGP11974A, respectively), in 1995, Froestl et al., demonstrated that the observed physiological effects of baclofen are stereoselective. They showed that the pharmacological action of baclofen is mediated by the R-(−)-enantiomer as R-(−)-baclofen (also known as Arbaclofen; Fig. 2) inhibits the binding of [^{3}H]-baclofen to $GABA_B$ receptors in cat cerebellum with an IC_{50} of 15 nM, while the S-(+)-enantiomer and racemic mixture display >100-fold and 3-fold higher IC_{50}, respectively (Froestl et al. 1995a). Many analogues of (R)-(−)-baclofen have been generated to interrogate the role of the carboxylic acid, amine, and p-chlorophenyl groups in attempts to increase potency and improve pharmacokinetic properties; as a consequence, more agonists, partial agonists, and antagonists have been discovered (Froestl 2010).

The first analogues that proved to be more potent than baclofen were generated by replacing the carboxylic acid portion of GABA with phosphinic acid residues to generate full agonists, CGP35024 (SKF97541) (Froestl et al. 1995a) and CGP27492 (Chapman et al. 1993) (Fig. 2), which have greater or equal affinity than baclofen for the $GABA_B$ receptor and IC_{50}s of 2 nM and 5 nM (Froestl et al. 1995a; Patel et al. 2001; Bon and Galvan 1996; Seabrook et al. 1990), respectively. Later SAR efforts investigated the replacement of the p-chlorophenyl group of baclofen with heterocycles. The absence of the chlorine atom from baclofen produces another potent $GABA_B$ receptor agonist, phenibut, and like baclofen, the majority of the agonist activity at the $GABA_B$ receptor is attributed to (R)-phenibut. Substitution with a 2-chlorothienyl group also provides an active albeit weaker agonist ($IC_{50} \sim 0.6$ μM) (Example 2c; Fig. 2) as determined in the [3H] baclofen displacement assay (Bolser et al. 1995). Further SAR and molecular modeling studies strongly implicated the p-chlorophenyl group (and its heteroaromatic substituents) as critical in the binding of baclofen and its analogues to the $GABA_B$ receptor (Costantino et al. 2001).

The phosphonous acid derivative, [(2R)-3-amino-2-fluoropropyl]phosphinic acid (AZD3355; Fig. 2) is a high affinity, non-brain penetrant analogue of baclofen that was developed by AstraZeneca and recently evaluated in clinical trials for the treatment of gastroesophageal reflux disease (GERD) under the generic name Lesogaberan® (Bredenoord 2009). AZD3355 has an EC_{50} of 9 nM compared to GABA's EC_{50} of 160 nM, and an increased binding affinity with a K_i of 5 nM versus GABA's 110 nM for inhibition of [^{3}H]-GABA binding in rat brain (Niazi et al. 2011).

It has been suggested that the low structural diversity of the existing orthosteric $GABA_B$ receptor ligands may be due to the conformational space having not been fully explored (Evenseth et al. 2019). In the early 2000s extensive mutagenesis studies on the extracellular domain of the $GABA_{B1}$ receptor subunit identified critical residues in LB1 and LB2 that are key for both agonist and antagonist binding (Galvez et al. 1999, 2000; Kniazeff et al. 2002). More recently, the first X-ray crystal structures of the $GABA_B$ receptor heterodimeric complex between the extracellular VFT domains of $GABA_{B1}$ and $GABA_{B2,}$ alone and in complex with bound agonists and antagonists were reported by Zuo et al., providing a more detailed understanding of how ligands act on the receptor (Geng et al. 2013). They demonstrated that in the inactive "apo" state and antagonist-bound state the VFT domains of both subunits adopt an open conformation whereas in the active "agonist-bound" state only the $GABA_{B1}$ subunit binds agonist and on doing so adopts a closed conformation.

Knowledge gained from these studies has since facilitated the development of a novel class of compounds that bind the orthosteric site of this receptor. In 2013, Colby et al. reported the discovery of $GABA_B$ receptor agonists comprised of β-hydroxy difluoromethyl ketones that represent the only structurally distinct $GABA_B$ receptor agonists as they lack the carboxylic acid or amino group of GABA (Example 10; Fig. 2) (Han et al. 2013). Additional analogues of the β-hydroxy difluoromethyl ketones have since been analyzed by the Colby laboratory, and docking models using the X-ray structures solved by Zuo et al. strongly suggest that these difluoromethyl ketones have similar binding modes to the orthosteric agonists (Sowaileh et al. 2018). Although some preliminary in vivo data suggest these compounds warrant further investigation as potential anxiolytic drugs (Han et al. 2013), their clinical utility has yet to be explored.

More recently, Mao and colleagues reported on Cryo-EM structures of the full-length inactive antagonist-bound and active agonist-bound in complex with $G\alpha_i$ protein of the $GABA_B$ receptor. This work further supports the findings that agonist binding stabilizes the closure of the $GABA_{B1}$ VFT domain (Geng et al. 2013). The Cryo-EM studies further revealed that agonist binding to $GABA_{B1}$ VFT domain induces rearrangement of the transmembrane (TM) interface between the $GABA_B$ subunits and this in turn promotes opening of the third intracellular loop in the $GABA_{B2}$ subunit allowing it to bind $G\alpha_i$ (Mao et al. 2020). Collectively, the structural studies of Zuo et al. and Mao et al. provide a deeper insight into $GABA_B$ receptor activation that will greatly assist in the design of novel modulators of the receptor.

6 Partial Agonists

Partial agonists are ligands that have varying degrees of intrinsic activities and affinity at their cognate receptors. They bind to and activate the receptor but elicit submaximal cell/tissue responses of the system relative to that produced by a full agonist. The naturally occurring GABA metabolite, γ-hydroxybutyric acid (GHB)

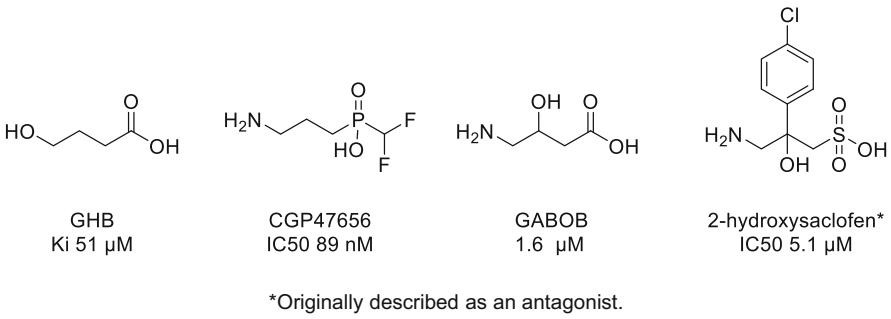


Fig. 3 Exemplar structures of $GABA_B$ receptor partial agonists

(Fig. 3), exhibits partial agonism at the $GABA_B$ receptor and is used clinically to treat symptoms of narcolepsy, alcohol dependence and withdrawal, and also used illicitly as a drug of abuse. However, experiments performed in $GABA_{B1}$ receptor null mice clearly show that not all the in vivo effects of GHB are $GABA_B$ receptor-mediated (Wellendorph et al. 2005). GHB has both low and high affinity receptor targets in the brain. The high affinity binding site is well characterized but has yet to be incontrovertibly identified. Whereas, it is well established that the $GABA_B$ receptor is the low affinity binding site where GHB acts as a partial agonist (Wong et al. 2004). Several studies demonstrated this finding including those of Mathivet et al. (1997); using binding experiments GHB was shown to have $K_i \sim 100$ μM compared to baclofen $K_i \sim 5$ μM (Mathivet et al. 1997); and Lingenhoehl et al. (1999); using recombinant systems expressing $GABA_{B1}/GABA_{B2}$ heteromer together with Kir3 channels in xenopus oocytes showed that GHB activated these receptors with an $EC_{50} \sim 5$ mM and a maximal stimulation of 69% relative to baclofen. Furthermore, three $GABA_B$ receptor competitive antagonists, CGP5426A, 2-hydroxysaclofen, and CGP35348 each completely blocked the GHB-evoked response further supporting GHB is a weak, partial agonist (Lingenhoehl et al. 1999).

Returning to the baclofen analogues, as mentioned CGP35024/SKF97541 (-γ-aminopropyl(methyl)phosphinic acid) is a potent agonist harboring a methyl substituent on the phosphinic acid moiety. Exchanging the methyl group for a difluoromethyl group produces CGP47656 (γ-aminopropyl(difluoromethyl)-phosphinic acid) (Fig. 3), rendering the molecule a partial agonist at the $GABA_B$ receptor as demonstrated by measuring binding affinities (Urwyler et al. 2005), the release of GABA from rat cortex (Froestl et al. 1995a; Gemignani et al. 1994), or the cholinergic twitch contraction in guinea pig ileum (Marcoli et al. 2000). Replacing the aromatic substituent at the 3-position of baclofen with a hydroxyl group also produces partial agonistic activity as seen in 4-amino-3-hydroxybutanoic acid (GABOB) (Fig. 3), with (R)-(−)-GABOB being tenfold less potent than racemic baclofen in binding experiments from rat brain isolates (Hinton et al. 2008).

As noted above, CGP35348 (Fig. 4) and 2-hydroxysaclofen (Fig. 3) (Kerr et al. 1988) have previously been described as $GABA_B$ receptor neutral competitive

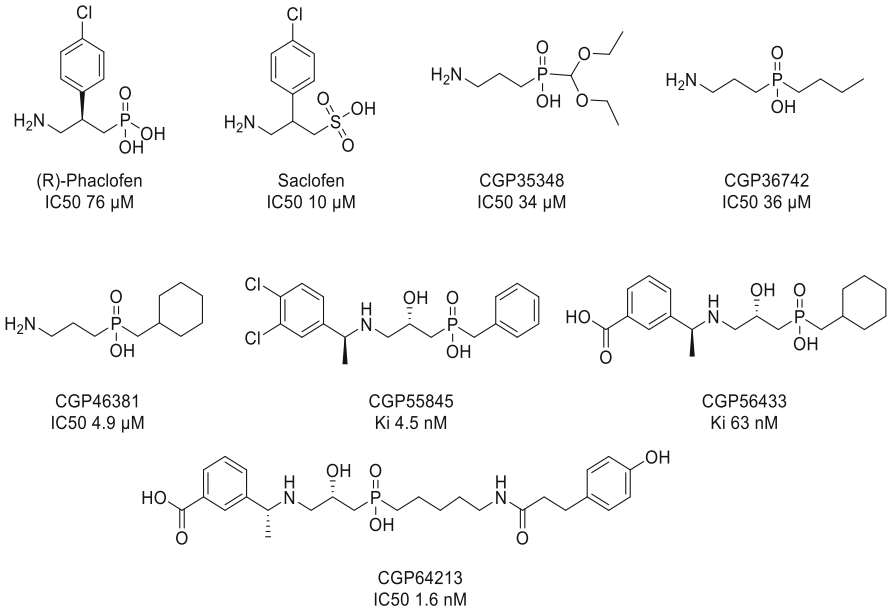


Fig. 4 Exemplar chemical structures of $GABA_B$ receptor antagonists

antagonists, having no intrinsic activity of their own and accordingly do not stimulate [^{35}S]-GTPγS-binding to membranes derived from CHO cells stably expressing the $GABA_B$ receptor. However, in the presence of CGP7930 or GS39783 (positive allosteric modulators, PAMs, of $GABA_B$ receptor) each "antagonist" stimulated [^{35}S]-GTPγS-binding to $GABA_B$ receptors with maximum efficiency of 31% and 35% of maximum GABA effect, respectively (Urwyler et al. 2005). A more sensitive assay measuring GABA/$GABA_B$ receptor-mediated inhibition of forskolin-stimulated cAMP accumulation revealed that CGP35348 and 2-hydroxysaclofen can have intrinsic partial agonistic activity in certain assay conditions that is enhanced by the PAMs. Thus, the PAMs revealed partial agonistic activity of compounds that otherwise appear to be devoid of intrinsic activity. Furthermore, the same experiments revealed that CGP7930 and GS39783 also possess intrinsic, low partial agonistic activity (Urwyler et al. 2005), an observation also reported by Binet et al. (Binet et al. 2004).

7 Antagonists

Following the 1979 discovery of a "bicuculline-insensitive, baclofen-sensitive" GABA receptor, efforts were immediately undertaken to design antagonists for this receptor. It was in the late 1980s that the first $GABA_B$ receptor antagonists were described. (R)-Phaclofen (Fig. 4), the phosphonic acid analogue of baclofen,

was one of the first discovered antagonists and was shown to block the slow inhibitory postsynaptic potential in the rat hippocampus establishing the physiological importance of this receptor (Dutar and Nicoll 1988). This discovery was closely followed by the discovery of saclofen and (S)-2-hydroxysaclofen (Fig. 3), sulphonic analogues of baclofen (Kerr et al. 1987). (R)-Phaclofen has a low affinity (~130 μM) for the receptor in radioligand binding experiments using rat brain membranes (Kerr et al. 1987), whereas (S)-2-hydroxysaclofen is tenfold more potent an antagonist at the $GABA_B$ receptor than (R)-phaclofen in this assay.

In addition to their significant contributions in interrogating $GABA_B$ receptor function and pharmacological activity, as with agonists, preclinical studies strongly support $GABA_B$ receptor antagonists having clinical importance in the treatment of various CNS disorders. $GABA_B$ receptor antagonists have been shown to suppress absence seizures in preclinical animal models of epilepsy (Bernasconi et al. 1992; Ostojić et al. 2013; Marescaux et al. 1992; Snead 3rd 1992), improve learning and memory (Bianchi and Panerai 1993; Lasarge et al. 2009; Mondadori et al. 1993) and have also been widely shown to have antidepressant-like activity in animal models (Cryan and Kaupmann 2005; Felice et al. 2012; Jacobson et al. 2018; Cryan and Slattery 2010; Frankowska et al. 2007; Mombereau et al. 2004; Nowak et al. 2006) along with a rescue of withdrawal from drugs of abuse-induced stress (Vlachou et al. 2011). Anhedonia, a common symptom of both psychostimulant withdrawal and depression, appears to be the key to the role of $GABA_B$ receptor in these disorders, as previously described by Markou and colleagues (Markou et al. 1992, 1998). Furthermore, the $GABA_B$ receptor has been shown to play a role in the regulation of glucose homeostasis in vivo (Bonaventura et al. 2012), $GABA_B$ receptor antagonism as well as receptor knockout mice shows improved glucose-stimulated insulin secretion (Bonaventura et al. 2008; Braun et al. 2004).

Following the discovery of phaclofen and 2-hydroxysaclofen, additional antagonists were discovered leading to CGP35348 (3-aminopropyl(diethoxymethyl)-phosphinic acid), a potent $GABA_B$ receptor antagonist and the first shown to penetrate the blood-brain barrier; CGP36742 (3-aminopropyl(n-butyl)phosphinic acid), the first orally bioavailable antagonist; and CGP46381, the phosphinic acid bearing a methylcyclohexyl group. However, like their predecessors, these compounds have low affinity (high μM range) for the $GABA_B$ receptor as does the chemically distinct SCH50911 (Bolser et al. 1995) (Fig. 5). As a result of SAR studies during the generation of these compounds, it was discovered that the nature of the alkyl substituent on the phosphinic acid plays a critical role in ligand activity. For example, a methyl substituent is present on the potent agonist CGP35024 (Fig. 2); when this is replaced with the difluoromethyl group of CGP47656 (3-aminopropyl(difluoromethyl)phosphinic acid), a decrease in activity at the $GABA_B$ receptor is observed with CGP47656 (Fig. 3) acting as a partial agonist (Froestl et al. 1995a; Urwyler et al. 2005; Gemignani et al. 1994; Marcoli et al. 2000). Increases in size of the substituent as with the butyl group in CGP36742 (Fig. 4) result in a derivative that displays antagonist activity at the $GABA_B$ receptor. Hence, very modest structural modifications to the baclofen core can lead to

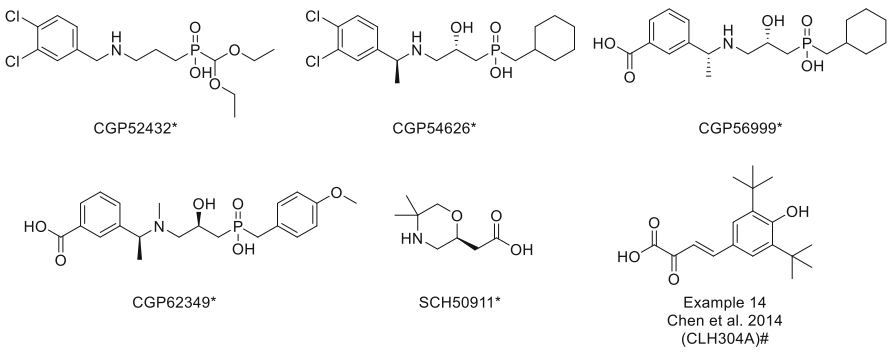


Fig. 5 Exemplar chemical structures of $GABA_B$ receptor inverse agonists

significant changes in ligand activity ranging from potent agonism to partial agonism to antagonism at the $GABA_B$ receptor (Pirard et al. 1995).

More potent antagonists have been developed since, displaying IC_{50} values in the nanomolar range. The radical shift in potency was achieved by substituting the amino group of existing $GABA_B$ modulators with benzyl substituents (3,4-dichlorobenzyl or 3-carboxybenzyl) as in CGP55845 and CGP56433, respectively. Other representatives of this generation of antagonists include CGP54626 (Fig. 4), and CGP62349, CGP52432, CGP56999, CGP54626, CGP64213 (Fig. 5); all highly potent antagonists and all demonstrating learning and memory-improving effects (Lasarge et al. 2009; Getova and Dimitrova 2007). These antagonists may also have significant clinical potential in absence epilepsy (Bernasconi et al. 1992; Marescaux et al. 1992; Snead 3rd 1992) as mice overexpressing the $GABA_{B1a}$ isoform exhibit characteristics associated with atypical absence epilepsy (Stewart et al. 2009).

8 Inverse Agonists

Given that GPCRs are believed to exist in equilibrium between inactive and active conformational states in which there is a continuum of structural conformations ranging from having no activity to being maximally active, these receptors have the potential to be active in the absence of an activating ligand, a phenomenon termed "constitutive activity." Ligands that stabilize the fully "inactive" conformation, thereby eliminating any intrinsic/constitutive activity the receptor may have, are referred to as "inverse agonists" (Berg and Clarke 2018; Kenakin 2004). Many GPCR-targeted drugs were initially characterized as "neutral" or "silent" antagonists as their discovery predated inverse agonism as a pharmacological concept. It is now estimated that at least 15% of compounds classified as antagonists have some

intrinsic activity and that these drugs confer their therapeutic efficacy by reducing constitutive receptor activity (Urwyler et al. 2005; Grunewald et al. 2002; Hirst et al. 2003; Mukherjee et al. 2006).

In the context of the $GABA_B$ receptor, constitutive receptor activity has been demonstrated to modulate neurotransmitter release and neuronal excitability in the absence of GABA. For example, in cerebellar Purkinje cells, $GABA_B$ receptor has been shown to interact with extracellular calcium ions to increase the sensitivity of the glutamate receptor 1 (mGluR1) to its endogenous ligand, glutamate, by forming a complex with the mGlu1R (Tabata et al. 2004). The use of a selective $GABA_B$ receptor inverse agonist could serve to eliminate enhanced glutamate mediated mGluR1 activity which has been identified as an avenue with therapeutic potential for the treatment of fragile X syndrome (Niswender and Conn 2010).

As noted, compounds CGP52432, CGP54626, CGP56999, CGP62349 (Fig. 5) are closely related, sharing the same core structure, and were originally identified as competitive antagonists at the $GABA_B$ receptor. As antagonists, these compounds have the ability to block GABA/$GABA_B$ receptor-mediated inhibition of forskolin-stimulated cAMP in $GABA_B$ receptor expressing recombinant systems. However, following receptor desensitization resulting from sustained exposure to GABA, the activity of this family of compounds switches from antagonism to inverse agonism as demonstrated by the CGP54626-promoted increase in cAMP production. The atypical SCH50911 antagonist that lacks large hydrophobic substituents behaved in a similar manner (Gjoni and Urwyler 2009). Likewise, the structurally distinct CLH304a previously reported as a negative allosteric modulator (NAM; Fig. 5) (Chen et al. 2014) has also since been reported to exhibit inverse agonist properties in the absence of an agonist (Sun et al. 2016).

9 Allosteric Modulators

While endogenous neurotransmitter GABA agonists (i.e., baclofen) and antagonists (i.e., phaclofen) bind to the orthosteric site (VFT domain) in the $GABA_{B1}$ subunit, it is now widely accepted that the $GABA_B$ receptor modulators identified so far act at allosteric sites (binding sites topographically distinct from the orthosteric ligand binding site) and bind the transmembrane region of the $GABA_{B2}$ subunit. Allosteric modulators (AMs) are basically classified as either positive allosteric modulators (PAMs) or negative allosteric modulators (NAMs). PAMs that possess intrinsic agonist activity are referred to as "ago-PAMs." A third class of allosteric ligand has been described that binds to the receptor but has no intrinsic activity and no apparent effect on endogenous ligand activity, hence it is referred to as a "silent allosteric modulator" (SAM) (Burford et al. 2013). Importantly, since orthosteric and allosteric ligands bind to topographically distinct sites of the receptor, both ligands can interact with the receptor simultaneously and thus, each ligand can affect the binding (binding cooperativity) and the intrinsic activity (activation cooperativity) of

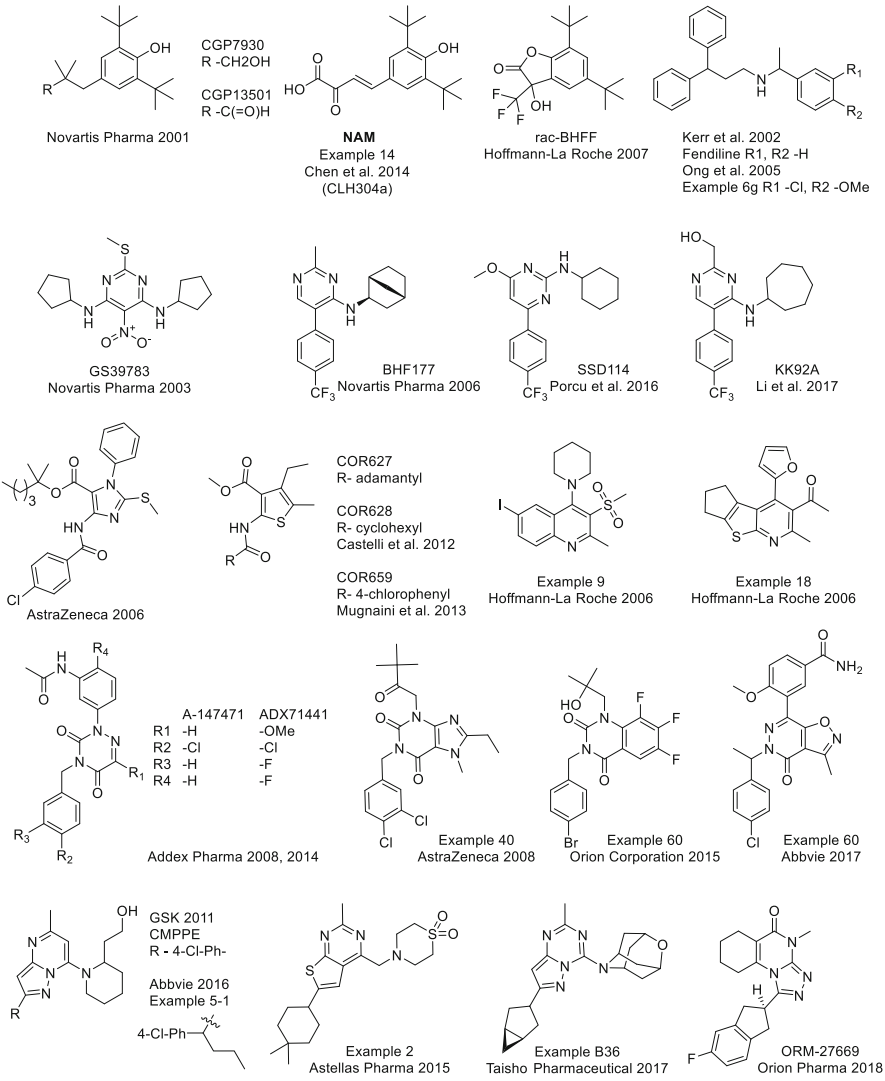
the other. Theoretical models describing these interactions have been discussed extensively elsewhere (Keov et al. 2011; May et al. 2004).

Allosteric sites are attractive therapeutic targets because molecules that bind to these sites can act in concert with an orthosteric ligand, and in doing so are believed to offer several advantages over the use of orthosteric ligands alone (Kenakin and Miller 2010). As allosteric modulators typically rely on the presence of the endogenous ligand, they have the ability to modify receptor activity in a spatial and temporal manner by acting in concert with the endogenous receptor ligand (Kenakin and Miller 2010). Therefore, allosteric modulators are believed to have the potential to induce fewer side effects, as they simply modulate endogenous ligand-mediated receptor activation. In addition, upon prolonged exposure, allosteric modulators are less likely to induce GPCR desensitization compared to an orthosteric agonist, and as such, are less likely to induce drug tolerance.

Allosteric modulators of the $GABA_B$ receptor have generated significant attention for their therapeutic potential in the treatment of alcohol and drug addiction, anxiety, depression, muscle spasticity, epilepsy, pain, and gastrointestinal disorders (Urwyler 2011). It is postulated that the use of a PAM (or ago-PAM) will achieve a more desirable pharmacological signaling profiling and physiological responses by enhancing GABA-mediated receptor signaling rather than artificially stimulating the receptor with an exogenous agonist such as baclofen. Furthermore, $GABA_B$ receptor allosteric modulators hold the promise of more favorable pharmacokinetics compared to baclofen including improved bioavalability and brain exposure as well as cytotoxicity. Hence, the potential advantages of $GABA_B$ receptor allosteric modulation have led to the development of numerous small molecule allosteric modulators, the majority of which are PAMs.

While many of the described $GABA_B$ receptor PAMs are structurally distinct, based on the core structure they can be sorted into several groups (Fig. 6; each row representing a distinct structural class). The discovery of $GABA_B$ receptor PAMs was pioneered and first reported by Novartis scientists, Urwyler and colleagues, in 2001. These researchers demonstrated that small molecule CGP7930 (2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol; discovered in a high throughput screening campaign) (Urwyler et al. 2001) potentiated GABA-stimulated [^{35}S]-GTPγS-accumulation in membrane preparations derived from CHO cells stably expressing the $GABA_B$ receptor. Using various combinations of wildtype and mutant $GABA_B$ subunits, Binet and colleagues investigated the mode of action of CGP7930, determining that the heptahelical domain (HD) of $GABA_{B2}$ was an absolute requirement for CGP7930 PAM action and that CGP7930 could also activate a truncated $GABA_{B2}$ subunit corresponding to the HD only (Binet et al. 2004).

In 2003, Novartis reported on another group of structurally distinct $GABA_B$ receptor PAMs, centered around GS39783 (*N,N′*-dicyclopentyl1–2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine). Like CGP7930, GS39783 was found to potentiate both affinity and maximal effects of GABA in biochemical and electrophysiological assay systems (Urwyler et al. 2003). Dupuis et al. studied point mutations in the TM region of $GABA_{B2}$ to identify the residues within the HD that



***NAM** CLH304a; an example of how subtle structural changes can change ligand activity

Fig. 6 Exemplar chemical structures of $GABA_B$ receptor allosteric modulators

interact with GS39783 and found that mutations G706T and A708P in TM6 were necessary and sufficient for GS39783 mediated agonist activation (Dupuis et al. 2006). Hence, both CGP7930 and GS39783 were found to bind to sites distinct from known agonist and antagonist receptor binding sites, and to require the presence of the $GABA_{B2}$ receptor subunit.

These findings prompted the pursuit of other molecules with similar PAM activities and consequently, numerous $GABA_B$ receptor allosteric modulators have been reported in the scientific and patent literature (accessible in SciFinder and Espacenet) over the past two decades. Roche scientists further developed the Novartis compounds by generating systematic modifications of CGP7930 structure and arrived at the bicyclic structure of rac-BHFF (Malherbe et al. 2008). Interestingly, it was found that both CGP7930 and rac-BHFF have intrinsic agonist activity, and distinct and differentiating ligand-induced signaling profiles compared to baclofen (Koek et al. 2013). Optimization of the genotoxic lead structure of the pyrimidine derivative of GS39783 led to the development of non-toxic $GABA_B$ receptor PAMs, such as BHF177 (N-[(1R,2R,4S)-bicyclo[2.2.1]heptan-2-yl]-2-methyl-5-[4-(trifluoromethyl)phenyl]-4-pyrimidinamine) reported by Novartis in 2006 (Floersheim et al. 2006). A decade later additional analogs from this series were reported by Porcu et al. (SSD114) (Porcu et al. 2016) and by our research group and collaborators Li et al. (KK-92A and approximately 100 additional analogs) (Li et al. 2017).

Substituted 5-membered heterocycles represent a substantial group of $GABA_B$ receptor PAMs, with the first examples of structurally novel modulators reported by AstraZeneca in patents aiming at the development of drugs for the treatment of gastrointestinal diseases (Bauer et al. 2005). Specific examples presented in the patents initially focused on imidazole derivatives that expanded in scope by scaffold hopping to cover other five-membered core heterocycles such as pyrazoles, oxazoles, and thiazoles. In 2011, a group led by Corelli identified COR627, COR628 (Castelli et al. 2012), and COR659 (Mugnaini et al. 2013) as $GABA_B$ receptor PAMs that displayed significant activity in vitro as $GABA_B$ receptor PAMs by potentiating [^{35}S]-GTPγS-binding induced by GABA while failing to exhibit intrinsic agonist activity. While the thiophene-based core of the active molecule differs from those reported by AstraZeneca, the substitution pattern resembles other representative molecules in this group.

Extensive work of Hoffman-La Roche resulted in the identification of additional classes of $GABA_B$ receptor PAMs disclosed in a series of patents published in 2006. The reported active molecules are based on a quinoline (Malherbe et al. 2006) or thieno[2,3-b]pyridine (Malherbe et al. 2007) as core heterocycles. A closely related set of $GABA_B$ receptor PAMs was reported in 2009 in an AstraZeneca patent (Cheng and Karle 2008). A separate group of $GABA_B$ receptor modulators represent a series of substituted triazinediones developed by Addex Pharma (Riguet et al. 2007). The Addex lead compound, ADX71441, is an orally available small molecule that demonstrated excellent preclinical efficacy and tolerability in several rodent models of pain, addiction, and overactive bladder (OAB) and has also proven efficacy in a genetic model of Charcot-Marie-Tooth Type 1A disease (CMT1A) (Cao and Zhang 2020).

In patents from 2008 and 2009 AstraZeneca scientists disclosed a new group of $GABA_B$ receptor PAMs based on bicyclic pyrimidinedione core, namely xanthines (Cheng et al. 2008a) and pteridine-2,4(1H,3H)-diones (Cheng et al. 2008b). Related structures were disclosed in 2015 by Orion Corporation (Prusis et al. 2015) and

Abbvie in 2017. In 2011, GlaxoSmithKline reported CMPPE, a novel moiety that positively modulated GABA-evoked in vitro [^{35}S]-GTPγS-binding signal with an EC_{50} value of 2.57 μM. The compound showed mild efficacy in a food consumption test in rats, modest in vivo potentiation of baclofen-induced muscle relaxation in mice, and poor metabolic stability in liver microsomal systems (Perdona et al. 2011). Other companies followed the CMPPE track with a range of modulators containing a modified core structure as the substitution pattern. Astellas Pharma reported a series of thieno[2,3-d]pyrimidines in 2015 (Shiraishi et al. 2014), whereas Abbvie (Faghih et al. 2016) and Richter Gedeon maintained pyrazolo[1,5-a]pyrimidinyl core in their series (WO 2018167630). In a single patent Taisho Pharmaceutical (Borza et al. 2018) covered analogs with the core heterocycle replaced by pyrazolo[1,5-a][1,3,5] triazine in addition to substituted pyrazolo[1,5-a]pyrimidines. ORM-27669, reported by Orion Pharma in 2017, with its tricyclic core structure containing [1,2,4]triazolo [4,3-a]pyrimidin-7(8H)-one represents a more original scaffold (de Miguel et al. 2019). Pretreatment with ORM-27669 reversed ethanol-induced neuroplasticity and attenuated ethanol drinking but had no effects on cocaine-induced neuroplasticity or self-administration.

Fendiline (Fig. 6) and its related arylalkylamines represent another unique structural class reported to be potential $GABA_B$ receptor PAMs. First reported as a non-selective calcium channel blocker and as a positive allosteric modulator of extracellular Ca^{2+} sensing receptors (CaSRs) (Nemeth et al. 1998), Fendiline is an FDA-approved (albeit obsolete) drug used in the treatment of coronary heart disease. Although not $GABA_B$ receptor specific, this compound is noteworthy as Ong and Kerr evaluated activity of Fendiline and its analogues as PAMs of $GABA_B$ receptors (Kerr et al. 2002, 2006) and demonstrated that the most potent analogue, (+)-N-1-(3-chloro-4-methoxyphenyl)ethyl-3,3-diphenylpropylamine) exhibited an EC_{50} of 30 nM in modulating baclofen-mediated function using grease gap recording in rat neocortical slices (Ong et al. 2005). However, direct action of Fendiline on $GABA_B$ receptor activity has been disputed (Urwyler et al. 2004) and further investigations are needed to determine the mechanism by which arylalkylamines enhance $GABA_B$ receptor-mediated responses.

$GABA_B$ receptor negative allosteric modulators (NAMs) have also been proposed as potential lead compounds for development into therapeutics for disorders such as CNS hyperexcitability-related disorders including epilepsy, anxiety, nerve damage, and low cognitive ability. Interestingly, modifications of $GABA_B$ receptor PAM CGP7930 (Fig. 6) led to discovery of the first $GABA_B$ receptor NAM, CLH304a, reported by Chen and colleagues in 2014 (Chen et al. 2014; Sun et al. 2016). CLH304a decreased agonist GABA-induced maximal effect of IP_3 production in HEK293 cells overexpressing $GABA_B$ receptor and Gαqi9 proteins without changing the EC_{50}. Moreover, it inhibited baclofen-induced $ERK_{1/2}$ phosphorylation and also blocked CGP7930-induced $ERK_{1/2}$ phosphorylation in HEK293 cells overexpressing $GABA_B$ receptor. This indicated that CLH304a (and some analogues) may be allosteric modulators, as orthosteric antagonists like CPG54626 are unable to attenuate PAM mediated signaling. Indeed, it was demonstrated that

the compounds of interest bound to an allosteric site, negatively regulating orthosteric agonist mediated signaling (Chen et al. 2014).

10 Probe Dependency

An important aspect of allosteric modulation to be taken into consideration is that the extent and direction (positive or negative) of the interaction between the orthosteric and allosteric ligands depends on which orthosteric ligand is present; a phenomenon known as "probe-dependency," this is important as many individual GPCRs respond to multiple endogenous ligands (May et al. 2004; Kenakin 2005). For the $GABA_B$ receptor, only having one known endogenous ligand, probe-dependency might be considered irrelevant. However, the potential combination of an allosteric modulator with a synthetic therapeutic such as baclofen must also consider the possibility of probe-dependent effects on receptor signaling and function.

Indeed, it has been demonstrated that baclofen shows improved efficacy and an increased therapeutic window when administered in combination with $GABA_B$ receptor PAMs (Maccioni et al. 2012). In preclinical studies, treatment with $GABA_B$ receptor PAMs GS39783 and rac-BHFF potentiated the activity of low doses of baclofen in relation to alcohol seeking behaviors (Maccioni et al. 2015). Hence, the ability of PAMs to reduce the effective dose of baclofen not only has the potential to improve efficacy in disease relevant measures, but also to expand the therapeutic window of this drug by reducing the accompanying adverse side effects. Thus, leveraging the probe-dependent effects of treatment with multiple receptor ligands has the potential to "fine-tune" receptor signaling and facilitate the development of improved strategies to target the $GABA_B$ receptor.

11 Biased Agonism/Functional Selectivity

It is well established that any given ligand for a GPCR does not simply possess a single defined efficacy; rather, a ligand possesses multiple efficacies, depending on the specific downstream signal transduction pathway being investigated. This diversity is believed to be the result of conformational changes induced in the GPCR that are ligand-specific and hence receptors can adopt various conformations that preferentially activate/modulate one signaling pathway to the exclusion of others; a phenomenon referred to as "functional selectivity" or "ligand bias" (Kenakin 2017; Smith et al. 2018; Spangler and Bruchas 2017). Conceptually, as with allosteric modulation, functional selectivity is an appealing mechanism of therapeutic intervention, as modulating only a select subset receptor signaling pathway may allow for the development of drugs that demonstrate therapeutic efficacy without recruiting pathways that lead to downstream adverse side effects (Kenakin and Miller 2010).

Functional selectivity can be achieved by modulating the receptor with a single ligand or with multiple ligands. Our own studies identified a PAM, namely KK-92A (4-(cycloheptylamino)-5-(4-(trifluoromethyl) phenyl)pyrimidin-2-yl) methanol) that exhibits pathway-selective differential modulation of $GABA_B$ receptor signaling when compared to the structurally related allosteric modulator BHF177 (Sturchler et al. 2017). Using recombinant cell-based systems overexpressing the $GABA_B$ receptor, KK-92A exhibited similar activity to BHF177 in potentiating GABA-induced $GABA_B$ receptor-mediated inhibition of forskolin-stimulated cAMP production and GABA-induced increase in intracellular Ca^{2+} levels. However, in contrast to BHF177, in the absence of GABA, KK-92A exhibited intrinsic activity with regard to $ERK_{1/2}$ phosphorylation achieving ~70% maximum efficacy relative to GABA maximum efficacy (Li et al. 2017), demonstrating ago-PAM activity and pathway-selective effects.

12 $GABA_B$ Receptor-Targeted Pharmaceuticals

The presence of functional $GABA_B$ receptors in mammalian brain and the gastrointestinal tract has been known for more than 30 years. Given the widespread distribution of GABA and the $GABA_B$ receptor in the CNS and periphery, it is not surprising that activation of the $GABA_B$ receptor provokes a host of physiological responses, and as a consequence, dysregulation of $GABA_B$ receptor activity was proposed to be associated with various CNS diseases such as mood disorders (Kalinichev et al. 2017; Li et al. 2015; Felice et al. 2012; Jacobson et al. 2018; Cryan and Slattery 2010), epilepsy (Billinton et al. 2001a; Teichgräber et al. 2009), addiction (Agabio and Colombo 2014, 2015; Agabio et al. 2018; Ranson et al. 2020; Maccioni et al. 2015), Parkinson's disease (Nambu 2012; Tyagi et al. 2015), Alzheimer's disease (Rice et al. 2019; Sun et al. 2020), Huntington's disease (Kim and Seo 2014) as well as peripheral diseases such as gastroesophageal reflux disease (GERD) (Clarke et al. 2018; Lehmann et al. 2010). More recently, GABA has emerged as a tumor signaling molecule in the periphery that controls tumor cell proliferation (Young and Bordey 2009; Zhang et al. 2014; Jiang et al. 2012), and stimulation of $GABA_B$ receptor signaling has been proposed as a novel target for the treatment and prevention of pancreatic cancer (Schuller et al. 2008; Schuller 2018; Al-Wadei et al. 2012). Numerous studies have shown potential clinical benefit of targeting the $GABA_B$ receptor in the treatment of various CNS and peripheral disorders, yet there is still only one therapeutic agent used clinically that selectively activates the $GABA_B$ receptor, namely baclofen (Lioresal®).

As discussed, baclofen was originally synthesized in 1962 by chemists at Ciba, Switzerland in an attempt to generate a more lipophilic, brain penetrant GABA mimetic (Keberle et al. 1964). It was assessed in the treatment of epilepsy but failed to show sufficient efficacy in the clinic. However, as a consequence of an incidental finding in that it had positive effects on muscle spasticity (Hudgson and Weightman 1971), baclofen (Lioresal®) has been in clinical use since 1972, gaining FDA

approval in 1977; long before its molecular target, the $GABA_B$ receptor was discovered and its mechanism of action identified. As previously mentioned, it has also shown therapeutic utility in a wide range of other off-label indications including addiction and was recently approved in Europe and Australia for the treatment of alcoholism (Agabio et al. 2018) but side effects such as sedation, nausea, muscle weakness, and rapid onset of tolerance limit its use (Kent et al. 2020).

With baclofen, an improvement over GABA regarding blood-brain barrier permeability was achieved, however, baclofen still has low brain penetration attributed to rapid efflux via the organic anion transporter (OAT3) (Ohtsuki et al. 2002). In parallel to Ciba's efforts in the 1960s to synthesize a GABA mimetic, a Russian team (Perekalin et al) synthesized a phenyl derivative of GABA, namely phenibut (-β-phenyl-γ-aminobutyric acid) that exhibits improved brain penetration over baclofen. Phenibut (Cirocard®) has been in clinical use in Russia and some Eastern European countries (not FDA-approved in USA) as a tranquilizer and cognition enhancer (nootropic) since the 1960s and is still used for these indications as well as for the treatment of mood and sleep disorders, PTSD, and a variety of neuropsychiatric diseases (Lapin 2001). However, phenibut suffers from many of the same liabilities as baclofen; sedation, muscle weakness, nausea, tolerance, and more recently has gained attention for its abuse potential (Jouney 2019).

Although baclofen has been in clinical use since 1972, it is far from an "ideal" drug; in addition to the unwanted side effects mentioned above, it also suffers from poor pharmacokinetic properties, including low brain penetration, limited absorption, short duration of action, rapid clearance from the blood, and narrow therapeutic window (Kent et al. 2020). Despite the lack of good "drug-like" qualities, the clinical success of baclofen has prompted numerous campaigns towards the identification and development of new and improved compounds that modulate the $GABA_B$ receptor and significant advances have been made. In 2009, XenoPort (now Arbor Pharmaceuticals) introduced Arbaclofen Placaril (XP19986), a transported prodrug of (R)-(−)-baclofen designed to possess a more favorable pharmacokinetic profile. Arbaclofen is absorbed throughout the intestinal tract and is rapidly converted to (R)-(−)-baclofen in tissues. It has been evaluated in Phase III clinical trials for GERD and multiple sclerosis, but these trials were discontinued in 2011 and 2013, respectively, due to lack of efficacy. It also reached Phase III trials in fragile X syndrome (FXS) but did not meet the primary outcome of improved social avoidance in FXS (Berry-Kravis et al. 2017). However, an extended release formula of Arbaclofen (Arbaclofen-ER; Ontinua®) developed by Osmotica is under FDA review as of July 2020 for the treatment of spasticity in multiple sclerosis. Also, two independent clinical trials evaluating benefit of Arbaclofen in children and adults with autism spectrum disorder (ASD) were initiated in 2019 (NCT03682978 and NCT03887676, respectively).

While XenoPort reported on Arbaclofen Placaril, AstraZeneca reported AZD3355 (Lesogaberan®; Fig. 2), a high affinity analogue of baclofen that was developed and evaluated in clinical trials for the treatment of GERD (Bredenoord 2009). AZD3355 is restricted peripherally and has a half-life of ~11 h in blood (Niazi et al. 2011). Unfortunately, Phase IIb clinical trials were terminated owing to

lack of efficacy in GERD patients. As AZD3355 is not brain penetrant and devoid of unwanted CNS effects, with no other adverse effects reported, indicating that it is safe in humans, it has been proposed that Lesogaberan® could be repurposed for the treatment of type 1 diabetes; targeting the $GABA_B$ receptor in β cells to promote β-cell survival (Tian et al. 2017).

GHB (γ-hydroxybutyric acid) is approved in some countries and used clinically for the treatment of narcolepsy-related catalepsy (Xyrem®) (Szabadi 2015) and rarely alcoholism (Alcover®) (Keating 2014). GHB also has the potential for abuse and is used illicitly as a recreational drug and intoxicant (Busardò and Jones 2015). Although GHB itself is not FDA-approved for medical use, the first generic version of Xyrem®, sodium oxybate (the sodium salt of GHB), recently (2017) received FDA approval to treat symptoms of narcolepsy including excessive daytime sleepiness and narcolepsy with cataplexy.

The first (and only to the best of our knowledge) clinical investigation of $GABA_B$ receptor antagonists was an open trial with SGS742 (CGP36742; Fig. 4) (Bullock 2005) (Froestl et al. 2004). Even though its potency is low ($IC_{50} \approx 40$ μM (Froestl et al. 1995b)), many preclinical studies showed benefit with SGS742 for spatial memory improvement (Helm et al. 2005), the treatment of depression (Nowak et al. 2006), and arrest of cortical seizures (Mares and Kubova 2008). The initial Phase II clinical trial, conducted in mild cognitive impairment patients, showed that SGS742 significantly improved attention, in particular choice reaction time and visual information processing as well as working memory (Froestl et al. 2004). However, a second Phase II trial was undertaken in mild to moderate Alzheimer's disease patients and no statistically significant improvement was detected prompting the termination of the development program. The clinical implications of modulating the $GABA_B$ receptor are outlined in Table 1.

13 Concluding Remarks

The $GABA_B$ receptor and its physiological roles are extremely complex, consequently, dysregulation of this receptor is involved in a broad range of diseases, and as such the $GABA_B$ receptor is considered a highly attractive therapeutic target for the development of new anti-epileptic, antidepressant, analgesic, and anxiolytic drugs, as well as for the treatment of cognitive disorders, drug addiction, and depression. However, at present only one compound that targets the orthosteric site of $GABA_B$ receptor is in clinical use, namely baclofen (Lioresal™); used to treat muscle spasticity in multiple sclerosis, and more recently used off-label for alcohol addiction. Unfortunately, side effects such as sedation, muscle weakness, nausea, and the lack of efficacy observed in other indications, i.e., fragile X syndrome, limit its therapeutic use. In addition to unwanted side effects baclofen also suffers from low brain penetration, limited absorption, rapid tolerance, short duration of action, and narrow therapeutic window. As described earlier, numerous small molecule agonists, antagonists, and allosteric modulators of the $GABA_B$

Table 1 Current therapeutic use and potential clinical utility of $GABA_B$ receptor modulators

Pharmacology	[a]Therapeutic use/[b]clinical potential	Approved drug/[c]clinical trial	References
Agonists/positive allosteric modulators	[a]Muscle rigidity and spasticity	Baclofen (Lioresal®) Arbaclofen-ER (Ontinua®)	(Francisco et al. 2001; Basmajian 1975; Korsgaard 1976; Coffey et al. 1993)
	[a]GERD	Baclofen (Lioresal®)	(Clarke et al. 2018; Lehmann et al. 2010; Ong and Kerr 1984; Lehmann 2009; Symonds et al. 2003)
	[a]Charcot-Marie tooth type 1A		(Cao and Zhang 2020; Dyer 2013)
	[a]PTSD/tranquilizer/nootropic	Phenibut (Cirocard®) (Eastern Europe only)	(Lapin 2001; Drake et al. 2003)
	[a]Cough suppression		(Chung 2015; Martvon et al. 2020)
	[a]Alcoholism and addiction	Sodium oxybate/GHB/(Alcover®), Baclofen (Lioresal®)	(Agabio and Colombo 2014, 2015; Agabio et al. 2018; Maccioni and Colombo 2019; Ranson et al. 2020)
	[b]Anxiety		(Kalinichev et al. 2017; Li et al. 2015)
	[b]Epilepsy		(Billinton et al. 2001a; Teichgräber et al. 2009)
	[b]Cataplexy	Sodium oxybate/GHB (Xyrem®)	(Black et al. 2014; Szabadi 2015)
	[b]Binge eating disorder		(Broft et al. 2007; Tsunekawa et al. 2019)
	[b]Parkinson's disease		(Nambu 2012; Tyagi et al. 2015)
	[b]Schizophrenia		(Glausier and Lewis 2017; Nair et al. 2020)
	[b]Huntington's disease		(Kim and Seo 2014; Kleppner and Tobin 2001)
	[b]Spatial learning and memory		(Modaberi et al. 2019; Sahraei et al. 2019)
	[b]Autism spectrum disorder (ASD)	Arbaclofen [c]NCT03682978, [c]NCT03887676	(Veenstra-VanderWeele et al. 2017; Frye 2014)
	[b]Fragile X syndrome (FXS)		(Berry-Kravis et al. 2017; Zhang et al. 2015)
	[b]Alzheimer's disease		(Rice et al. 2019; Sun et al. 2020)
	[b]Analgesic (fibromyalgia)	[c]NCT03092726	(Neto et al. 2006; Enna and McCarson 2006; Murai et al. 2019)
	[b]Pancreatic cancer		(Young and Bordey 2009; Zhang et al. 2014; Jiang et al. 2012;

(continued)

Table 1 (continued)

Pharmacology	[a]Therapeutic use/[b]clinical potential	Approved drug/[c]clinical trial	References
			Schuller et al. 2008; Schuller 2018; Al-Wadei et al. 2012)
	[b]Type 1 diabetes		(Tian et al. 2017)
Antagonists/ negative allosteric modulators	[b]Depression/mood disorders		(Cryan and Kaupmann 2005; Felice et al. 2012; Jacobson et al. 2018)
	[b]Type 2 diabetes		(Bonaventura et al. 2008, 2012; Braun et al. 2004)
	[b]Absence epilepsy/ seizures		(Bernasconi et al. 1992; Ostojić et al. 2013)
	[b]Mild cognitive impairment and memory		(Lasarge et al. 2009; Mondadori et al. 1993)
	[b]Succinic semi-aldehyde dehydrogenase (SSADH) deficiency	[c]NCT02019667	(Cortez et al. 2004; Didiášová et al. 2020)

[a]Therapeutic use
[b]Clinical potential
[c]Clinical trail

receptor have been described in the scientific and patent literature that have been developed for their therapeutic potential; positive allosteric modulators, for example, have been proposed to mitigate the unwanted side effects and reduce tolerance but have yet to be approved for clinical use. Hence, identification of novel drugs targeting the $GABA_B$ receptor that display improved efficacy and pharmacokinetic properties and with a safer side effect profile is the subject of intense research and many industrial scale drug discovery efforts.

As mentioned, the multifaceted $GABA_B$ receptor is extremely complex. However, the same complexity that has historically hindered development of $GABA_B$ receptor-targeted therapeutics now provides the potential for discovery of $GABA_B$ receptor disease-specific therapeutics. For example, $GABA_B$ receptor subtype-selective ligands are highly desirable not only to dissect the physiological role of the predominant receptor subtypes, $GABA_{B1(a)/2}$ and $GABA_{B1(b)/2}$, but also to facilitate the development of more finely-tuned mode-of-action drugs to treat various diseases. From a drug discovery perspective, it may be possible to selectively modulate $GABA_{B(1a)}$ containing heteroreceptors by targeting their sushi domains, case in point; amyloid precursor protein (APP) binds to the N-terminal sushi domain of $GABA_{B(1a)}$ and acts as an axonal trafficking factor for $GABA_B$ receptors, it has been proposed that prevention of APP binding to this domain may interfere with $GABA_B$ receptor-mediated inhibition of glutamate release and thereby enhance cognitive function in patients with Alzheimer's disease and intellectual disabilities. Likewise, the discovery of functionally selective ligands for the different $GABA_B$ receptor effectors would provide powerful tools to identify a unique signaling profile that results in the desired in vivo effects without recruiting the adverse side effects.

Alternatively, recent biophysical and structural studies have greatly improved our understanding of the structural basis of $GABA_B$ receptor activation and modulation, and proteomic studies have identified receptor-associated proteins that work in concert with the receptor to orchestrate a variety of molecularly and functionally distinct multiprotein "signalosome" complexes, while providing spatiotemporal control of receptor activity. These findings also present new opportunities for drug discovery, modulating specific protein:protein interactions mediated through sushi domains of $GABA_{B1(a)}$ (as outlined above), C-terminal domain of $GABA_B1$ and/or $GABA_{B2}$; or KCTD subunits, all present potential target sites for designing drugs that selectively interfere with receptor function for disease-specific therapeutic intervention.

Thus, the successful collaboration between medicinal chemistry and pharmacology together with significant advances in our understanding of $GABA_B$ receptor structure and activation mechanisms has drug hunters well-poised for the discovery and development of chemically and mechanistically novel therapeutics targeting the multi-tasking $GABA_B$ receptor for the treatment of a wide variety of disease states.

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