GABA_B

Overview: Functional GABA_B receptors (nomenclature agreed by NC-IUPHAR Subcommittee on GABA_B receptors, Bowery et al., 2002; see also Pin et al., 2007) are formed from the heterodimerization of two similar 7TM subunits termed GABA_B1 and GABA_B2 (Bowery et al., 2002; Pin et al., 2004; Emson, 2007; Pin et al., 2007; Ulrich and Bettler, 2007). GABA_B1 receptors are widespread in the CNS and regulate both pre- and post-synaptic activity. The GABA_B1 subunit, when expressed alone, binds both antagonists and agonists, but the affinity of the latter is generally 10-100-fold less than for the native receptor. The GABA_B1 subunit when expressed alone is not transported to the cell membrane and is non-functional. Co-expression of GABA_B1 and GABA_B2 subunits allows transport of GABA_B2 to the cell surface and generates a functional receptor that can couple to signal transduction pathways such as high-voltage-activated Ca^{2+} channels (Ca_{2.1}, Ca_{2.2}), or inwardly rectifying potassium channels (Kir3) (Bowery and Enna, 2000; Bowery et al., 2002; Bettler et al., 2004). The GABA_B2 subunit also determines the rate of internalisation of the dimeric GABA_B receptor (Hannan et al., 2011). The GABA_B2 subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) versus flytrap module (VTM), whereas the GABA_B2 subunit mediates G-protein coupled signalling (Bowery et al., 2002, Pin et al., 2004). The two subunits interact by direct allosteric coupling (Monnier et al., 2011) such that GABA_B2 increases the affinity of GABA_B1 for agonists and reciprocally GABA_B1 facilitates the coupling of GABA_B2 to G proteins (Pin et al., 2004; Kubo and Tatemaya, 2005). GABA_B1 and GABA_B2 subunits assemble in a 1:1 stoichiometry by means of a coiled-coil interaction between α-helices within their carboxy-terminus that masks an endoplasmic reticulum retention motif (RXR) within the GABA_B2 subunit but other domains of the proteins also contribute to their heteromerization (Bettler et al., 2004; Pin et al., 2004). Recent evidence indicates that higher order assemblies of GABA_B receptor comprising dimers of heterodimers occur in recombinant expression systems and in vivo and that such complexes exhibit negative functional cooperativity between heterodimers (Pin et al., 2009; Comps-Agras et al., 2011). Adding further complexity, KCTD (potassium channel tetramerization proteins) 8, 12, 12b and 16 associate as tetramers with the carboxy terminus of the GABA_B2 subunit to impart altered signalling kinetics and agonist potency to the receptor complex (Barot et al., 2010; Schwerik et al., 2010 and reviewed by Pinard et al., 2010). Four isoforms of the human GABA_B2 subunit have been cloned. The predominant GABA_B2GABA_B2 and GABA_B2GABA_B1b isoforms, which are most prevalent in neonatal and adult brain tissue respectively, differ in their ECD sequences as a result of the use of alternative transcription initiation sites. GABA_B2GABA_B2-containing heterodimers localise to distal axons and mediate inhibition of glutamate release in the CA3-CA1 terminals, and GABA_B2 release onto the layer 5 pyramidal neurons, whereas GABA_B2GABA_B1b-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition (Vigot et al., 2006; Pérez-Garcia et al., 2006). Isoforms generated by alternative splicing are GABA_B2GABA_B2 that differs in the ECD, and GABA_B1GABA_B2 which is a truncated protein that can heterodimerize with the GABA_B2 subunit but does not constitute a functional receptor. Only the 1a and 1b variants are identified as components of native receptors (Bowery et al., 2002). Additional GABA_B1 subunit isoforms have been described in rodents and humans (Lee et al., 2010 and reviewed by Bettler et al., 2004).

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>GABA_B</th>
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<tbody>
<tr>
<td>Ensembl ID</td>
<td>GABA_B1 ENSG000000237051; GABA_B2 ENSG00000136928</td>
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<tr>
<td>Principal transduction</td>
<td>C_60</td>
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<tr>
<td>Selective agonists</td>
<td>3-APPA (CGP27492, 5 nM), 3-APMPA (CGP35024, 16 nM), (R)-baclofen (32 nM), CGP44532 (45 nM)</td>
</tr>
<tr>
<td>Selective antagonists</td>
<td>CGP62349 (2.0 nM), CGP55845A (6 nM), SCH50911 (3 μM), 2-hydroxy-s-(−)-saclofen (11 μM), CGP35348 (27 μM)</td>
</tr>
<tr>
<td>Probes (K_a)</td>
<td>[3H]3-[(R)-(−)]-baclofen, [3H]CGP54626 (1.5 nM; Bitiger et al., 1992), [3H]CGP62349 (0.9 nM, Keir et al., 1999), [3H]CGP64213 (1 nM, Galvez et al., 2000), [3H]CGP71872 (K = 0.5 nM, Belley et al., 1999)</td>
</tr>
</tbody>
</table>

Potencies of agonists and antagonists listed in the table, quantified as IC_{50} values for the inhibition of [3H]CGP27492 binding to rat cerebral cortex membranes, are from Froestl and Michel (1997), Bowery et al. (2002) and Froestl (2011). Radioligand K_a values relate to binding to rat brain membranes. CGP71872 is a photoaffinity ligand for the GABA_B2 subunit (Belley et al., 1999). CGP27492, CGP35024 and CGP44532 act as antagonists at human GABA_B1 receptors, with potencies in the low micromolar range (Froestl, 2011). In addition to the ligands listed in the table, Ca^{2+} binds to the VTM of the GABA_B2 subunit to act as a positive allosteric modulator of GABA (Galvez et al., 2000). In cerebellar Purkinje neurons, the interaction of Ca^{2+} with the GABA_B2 receptor enhances the activity of mGlu, through functional cross-talk involving G-protein Gi/ρ subunits (Tabata et al., 2004; Rives et al., 2009). Synthetic positive allosteric modulators with low, or no, intrinsic activity include CGP7930, GS39783, BHF177 and (+)-BF177 (Bettler et al., 2004; Binet et al., 2004; Adams and Lawrence, 2007; Froestl, 2011). The site of action of CGP7930 and GS39783 appears to be on the heptahedral domain of the GABA_B2 subunit (Pin et al., 2004; Dupuis et al., 2006). In the presence of CGP7930, or GS39783, CGP35348 and 2-hydroxy-saclofen behave as partial agonists (Froestl, 2011). Knock-out of the GABA_B2 subunit in C57B mice causes the development of severe tonic-clonic convulsions that prove fatal within a month of birth, whereas GABA_B2-c BALB/c mice, although also displaying spontaneous epileptiform activity, are viable. The phenotype of the latter animals additionally includes hyperalgesia, hyperlocomotion (in a novel, but familiar, environment), hyperdopaminergia, memory impairment and behaviours indicative of anxiety (Enna and Bowery, 2004; Vacher et al., 2006). A similar phenotype has been found for GABA_B2-c BALB/c mice (Gassmann et al., 2004).
Abbreviations: 3-APMPA (CGP35024), 3-amino-propyl-(p-methyl)-phosphonic acid; 3-APPA (CGP27492), 3-amino-propyl-phosphonic acid; (+)-BBFF, (-)-7,5-di-tert-butyl-3-hydroxy-3-trifluoromethyl-3H-benzofuran-2-one; BHF177, (1R,2R,4S)-biciclo[2.2.1]hept-2-yl-[2-methyl-5-[4-(trifluoromethyl)phenyl]-4-pyrimidinamine; CGP7930, 2,6-Di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol; CGP35348, p-(3-amino-propyl)-p-diethoxymethyl-phosphonic acid; CGP44532, 3-amino-2-hydroxypropylmethylphosphonic acid; CGP54626, 8-[R,R]-[3-[1-(3,4-dichlorophenyl)ethyl][ amino]-2-hydroxypropyl][cycohexylmethyl]phosphonic acid; CGP55845A, 3-[[1-((3,4-dichlorophenyl)ethyl)amino]-2-hydroxypropyl][cyclohexylmethyl]phosphonic acid; CGP62349, 3-[[1-[3-(methoxyphenyl)ethyl]hydroxyphosphinyl][2-(S)-hydroxypropyl]amino]ethyl-benzoic acid; CGP64213, 3-[[1-[3-(3-iodo-4-hydroxyphenyl)ethyl]carboxamido]pentoxyhydrophosphoryl][2-(S)-hydroxypropyl]amino]ethyl-benzoic acid; CGP71872, 3-[[1-(R)-3-[[4-(azido-2-hydroxy-5-iodobenzoylamino)pentyl]hydroxophosphoryl]-2-(S)-hydroxypropyl]amino]ethyl-benzoic acid; GS39783, N,N’-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine; SCH50911, (+)-(2S,5,5)-dimethyl-2-morpholineneacetic acid; VTM, Venus flytrap module

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References


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