$GABA_B$

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). 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 $GABA_{B1}$ to the cell surface and generates a functional receptor that can couple to signal transduction pathways such as high-voltage-activated Ca^{2+} channels ($Ca_v2.1$, $Ca_v2.2$), or inwardly rectifying potassium channels (Kir3) (Bowery and Enna, 2000; Bowery *et al*., 2002; Bettler *et al*., 2004). The $GABA_{B1}$ subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) venus 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 allosterically in 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 Tateyama, 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-termini that masks an endoplasmic reticulum retention motif (RXRR) within the $GABA_{B1}$ subunit but other domains of the proteins also contribute to their heteromerization (Bettler *et al*., 2004; Pin *et al*., 2004). Four isoforms of the human $GABA_{B1}$ subunit have been cloned. The predominant $GABA_{B1(a)}$ and $GABA_{B1(b)}$ 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. $GABA_{B1(a)}$-containing heterodimers localize to distal axons and mediate inhibition of glutamate release in the CA3–CA1 terminals, and GABA release onto the layer 5 pyramidal neurons, whereas $GABA_{B1(b)}$-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition (Pérez-Garci *et al*., 2006; Vigot *et al*., 2006). Isoforms generated by alternative splicing are $GABA_{B1(c)}$ that differs in the ECD, and $GABA_{B1(e)}$, 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 (reviewed by Bettler *et al*., 2004).

Nomenclature	$GABA_B$
Ensembl ID	$GABA_{B1}$ ENSG00000168760; $GABA_{B2}$ ENSG00000136928
Principal transduction	$G_{i/o}$
Selective agonists	3-APPA (CGP27492, 5 nM), 3-APMPA (CGP35024, 16 nM), (*R*)-(-)-baclofen (32 nM), CGP44532 (45 nM)
Selective antagonists	CGP62349 (2.0 nM), CGP55845 (6 nM), SCH50911 (3 μM), 2-hydroxy-s-(-)-saclofen (11 μM), CGP35348 (27 μM)
Probes (K_D)	[^{3}H](*R*)-(-)-baclofen, [^{3}H]CGP54626 (1.5 nM, Bittiger *et al*., 1992), [^{3}H]CGP62349 (0.9 nM, Kier *et al*., 1999), [^{125}I]CGP64213 (1 nM, Galvez *et al*., 2000), [^{125}I]CGP71872 (K_i = 0.5 nM, Belley *et al*., 1999)

Potencies of agonists and antagonists listed in the table, quantified as IC_{50} values for the inhibition of [^{3}H]CGP27492 binding to rat cerebral cortex membranes, are from Froestl and Mickel (1997) and Bowery *et al*. (2002). Radioligand K_D values relate to binding to rat brain membranes. CGP71872 is a photoaffinity ligand for the $GABA_{B1}$ subunit (Belley *et al*., 1999). In addition to the ligands listed in the table, Ca^{2+} binds to a site on the $GABA_{B1}$ subunit to act as a positive allosteric modulator of GABA (Galvez *et al*., 2000). In cerebellar Purkinje neurones, the interaction of Ca^{2+} with the $GABA_B$ receptor enhances the activity of mGlu1, most probably via a direct association between the two receptors (Tabata *et al*., 2004). Synthetic positive allosteric modulators with little, or no, intrinsic activity include CGP7930 and GS39783 (reviewed by Bettler *et al*., 2004; Adams and Lawrence, 2007). Their site of action appears to be on the heptahelical domain of the $GABA_{B2}$ subunit (Pin *et al*., 2004; Dupuis *et al*., 2006). Knockout of the $GABA_{B1}$ subunit in C57B mice causes the development of severe tonic-clonic convulsions that prove fatal within a month of birth, whereas $GABA_{B1}^{-/-}$ 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 not 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 $GABA_{B2}^{-/-}$ BALB/c mice (Gassmann *et al*., 2004).

Abbreviations: 3-APMPA (CGP35024), 3-amino-propyl-(P-methyl)-phosphinic acid; **3-APPA (CGP27492)**, 3-amino-propyl-phosphinic acid; **CGP7930**, 2,6-Di-*tert*-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol; **CGP35348**, p-(3-aminopropyl)-P-diethoxymethylphosphinic acid; **CGP44532**, 3-amino-2-hydroxypropylmethylphosphinic acid; **CGP54626**, [*S*-(*R*,*R*)]-[3-[[1-(3,4-dichlorophenyl)ethyl]amino]-2-hydroxypropyl](cyclohexylmethyl)phosphinic acid; **CGP55845**, 3-[-1-(*S*)-(3,4-dichlorphenyl)-ethyl]amino-2(*S*)-hydroxypropyl-(P-benzyl)-phosphinic acid; **CGP62349**, [3-[1-*R*-[[3-(methoxyphenylmethyl)hydroxyphosphinyl]-2(5)-hydroxypropyl]amino]ethyl]-benzoic acid; **CGP64213**, [3-[-(*R*)-[[3-5*N*-[1-[2-[[3-iodo-4-hydroxyphenyl]ethyl]carboxamido]pentyl]hydroxyphosphinyl]-2(*S*)-hydroxy-propyl]amino]ethyl-benzoic acid; **CGP71872**, 3-(1-(*R*)-(3-((5-(4-azido-2-hydroxy-5-iodobenzoylamino)pentyl)hydroxyphosphoryl)-2-(*S*)-hydroxypropylamino)ethyl)benzoic acid; **GS39783**, *N*,*N*′-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine; **SCH90511**, (+)-(2*S*)-5,5-dimethyl-2-morpholineacetic acid

Further Reading

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