GABA\(_B\) receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

Abstract

Functional GABA\(_B\) receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on GABA\(_B\) receptors [11, 72]) are formed from the heterodimerization of two similar 7TM subunits termed GABA\(_B1\) and GABA\(_B2\) [11, 71, 28, 72, 85]. GABA\(_B\) receptors are widespread in the CNS and regulate both pre- and postsynaptic 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. 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\(_{v}\)2.1, Ca\(_{v}\)2.2), or inwardly rectifying potassium channels (Kir3) [12, 11, 5]. 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 [11, 71, 40, 39]. The two subunits interact by direct allosteric coupling [63], 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 [71, 54, 39]. 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 [5, 71, 15]. 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 [70, 22]. 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 [84, 3, 79] and are reviewed by [73]. The molecular complexity of GABAB receptors is further increased through association with trafficking and effector proteins [Schwenk et al., 2016, Nature Neuroscience 19(2): 233-42] and reviewed by [69]. Four isoforms of the human GABA\(_B1\) subunit have been cloned. The predominant GABA\(_B1a\) and GABA\(_B1b\) 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$_{B1\alpha}$-containing heterodimers localise 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$_{B1\beta}$-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition [75, 89]. Only the 1a and 1b variants are identified as components of native receptors [11]. Additional GABA$_B_1$ subunit isoforms have been described in rodents and humans [55] and reviewed by [5].

Contents

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Database links

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http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1919
KCTD12
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References


47. Jones KA, Borowsky B, Tamm DA, Craig DA, Durkin MM, Dai M, Yao WJ, Johnson M, Gunwaldsen C and Huang LY et al. (1998) GABA(B) receptors function as a heteromeric assembly of the subunits GABA(B)R1 and GABA(B)R2. Nature 396: 674-9 [PMID:9872315]


