

## GABA<sub>B</sub> receptors in GtoPdb v.2021.2

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### Abstract

Functional GABA<sub>B</sub> receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on GABA<sub>B</sub> receptors [11, 71]**) are formed from the heterodimerization of two similar 7TM subunits termed GABA<sub>B1</sub> and GABA<sub>B2</sub> [11, 70, 28, 71, 87]. GABA<sub>B</sub> receptors are widespread in the CNS and regulate both pre- and postsynaptic activity. The GABA<sub>B1</sub> 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<sub>B1</sub> and GABA<sub>B2</sub> subunits allows transport of GABA<sub>B1</sub> to the cell surface and generates a functional receptor that can couple to signal transduction pathways such as high-voltage-activated Ca<sup>2+</sup> channels (Ca<sub>v</sub>2.1, Ca<sub>v</sub>2.2), or inwardly rectifying potassium channels (Kir3) [12, 11, 5]. The GABA<sub>B1</sub> subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) venus flytrap module (VTM), whereas the GABA<sub>B2</sub> subunit mediates G protein-coupled signalling [11, 70, 40, 39]. The cryo-electron microscopy structures of the human full-length GABA<sub>B1</sub>-GABA<sub>B2</sub> heterodimer have been solved in the inactive apo state, two intermediate agonist-bound forms and an active state in which the heterodimer is bound to an agonist and a positive allosteric modulator [81]. The positive allosteric modulator binds to the transmembrane dimerization interface and stabilizes the active state. Recent evidence indicates that higher order assemblies of GABA<sub>B</sub> receptor comprising dimers of heterodimers occur in recombinant expression systems and *in vivo* and that such complexes exhibit negative functional cooperativity between heterodimers [69, 22]. Adding further complexity, KCTD (potassium channel tetramerization proteins) 8, 12, 12b and 16 associate as tetramers with the carboxy terminus of the GABA<sub>B2</sub> subunit to impart altered signalling kinetics and agonist potency to the receptor complex [86, 3, 79] and are reviewed by [72]. The molecular complexity of GABA<sub>B</sub> receptors is further increased through association with trafficking and effector proteins [80] and reviewed by [68]. The predominant GABA<sub>B1a</sub> and GABA<sub>B1b</sub> 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<sub>B1a</sub>-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<sub>B1b</sub>-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition [74, 91]. Amyloid precursor protein (APP) and soluble APP (sAPP) bind to the N-terminal sushi domain of the GABA<sub>B1a</sub> isoform to regulate axonal trafficking of GABA<sub>B</sub> receptors and release of neurotransmitters [76].

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##### KCTD16

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