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GABA$_B$ receptors in GtoPdb v.2025.3

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Abstract

Functional GABA$_B$ receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on GABA$_B$ receptors [11, 74]**) are formed from the heterodimerization of two similar 7TM subunits termed GABA$_{B1}$ and GABA$_{B2}$ [11, 73, 29, 74, 90]. 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, 73, 42, 41]. The cryo-electron microscopy structures of the human full-length GABA$_{B1}$-GABA$_{B2}$ 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 [84]. Phospholipids bound within the central cavity of the transmembrane domains stabilize the inactive state. The positive allosteric modulator binds to the transmembrane interface and stabilizes the active state. Recent evidence indicates that higher order assemblies of GABA$_B$ receptors comprising dimers of heterodimers occur in recombinant expression systems and *in vivo*, and that such complexes exhibit negative functional cooperativity between heterodimers [72, 23]. 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 [89, 3, 82] and are reviewed by [75]. The molecular complexity of GABA$_B$ receptors is further increased through association with trafficking and effector proteins [83] and reviewed by [71]. 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$_{B1a}$-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$_{B1b}$-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition [77, 94]. Amyloid precursor protein (APP) and soluble APP (sAPP) bind to the N- terminal sushi domain of the GABA$_{B1a}$ isoform to regulate axonal trafficking of GABA$_B$ receptors and release of neurotransmitters [79]. AJAP1 (Q9UKB5) is a dendritic protein that trans-synaptically recruits GABA$_{B1a}$-containing receptors to presynaptic sites [31]. Missense variants in *GABABR* and *AJAP1* genes as well as autoantibodies link receptor dysfunction to neurodevelopmental disorders and epileptic encephalopathies [17, 31, 57].

Contents

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