

GABA_B receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

Bernhard Bettler¹, Norman G. Bowery², John F. Cryan³, Sam J. Enna⁴, David H. Farb⁵, Wolfgang Foestl⁶, Klemens Kaupmann⁶ and Jean-Philippe Pin⁷

1. University of Basel, Switzerland
2. GlaxoSmithKline, Italy
3. University College Cork, Ireland
4. University of Kansas Medical Center, USA
5. Boston University, USA
6. Novartis Institutes for Biomedical Research, Switzerland
7. Université de Montpellier, France

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 Ca²⁺ channels (Ca_v2.1, Ca_v2.2), 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 GABA_B 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_{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 [75, 89]. Only the 1a and 1b variants are identified as components of native receptors [11]. Additional GABA_{B1} subunit isoforms have been described in rodents and humans [55] and reviewed by [5].

Contents

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