GABA<sub>A</sub> receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

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Abstract

The GABA<sub>A</sub> receptor is a ligand-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT<sub>3</sub> and strychnine-sensitive glycine receptors. GABA<sub>A</sub> receptor-mediated inhibition within the CNS occurs by fast synaptic transmission, sustained tonic inhibition and temporally intermediate events that have been termed ‘GABA<sub>A</sub>, slow’ [41]. GABA<sub>A</sub> receptors exist as pentamers of 4TM subunits that form an intrinsic anion selective channel. Sequences of six α, three β, three γ, one δ, three ρ, one ε, one π and one θ GABA<sub>A</sub> receptor subunits have been reported in mammals [273, 232, 231, 278]. The π-subunit is restricted to reproductive tissue. Alternatively spliced versions of many subunits exist (e.g. α4- and α6- (both not functional) α5-, β2-, β3- and ρ2), along with RNA editing of the α3 subunit [67]. The three ρ-subunits, (ρ1-3) function as either homo- or hetero-oligomeric assemblies [354, 46]. Receptors formed from ρ-subunits, because of their distinctive pharmacology that includes insensitivity to bicuculline, benzodiazepines and barbiturates, have sometimes been termed GABA<sub>C</sub> receptors [354], but they are classified as GABA<sub>A</sub> receptors by NC-IUPHAR on the basis of structural and functional criteria [14, 232, 231].

Many GABA<sub>A</sub> receptor subtypes contain α-, β- and γ-subunits with the likely stoichiometry 2α.2β.1γ [164, 232]. It is thought that the majority of GABA<sub>A</sub> receptors harbour a single type of α- and β -subunit variant. The α1β2γ2 hetero-oligomer constitutes the largest population of GABA<sub>A</sub> receptors in the CNS, followed by the α2β3γ2 and α3β3γ2 isoforms. Receptors that incorporate the α4- α5-or α6-subunit, or the β1-, γ1-, γ3-, δ-, ε-, and ρ-subunits, are less numerous, but they may nonetheless serve important functions. For example, extrasynaptically located receptors that contain α6- and δ-subunits in cerebellar granule cells, or an α4- and δ-subunit in dentate gyrus granule cells and thalamic neurones, mediate a tonic current that is important for neuronal excitability in response to ambient concentrations of GABA [205, 268, 79, 17, 283]. GABA binding occurs at the β+/α- subunit interface and the homologous γ+/α- subunits interface creates the benzodiazepine site. A second site for benzodiazepine binding has recently been postulated to occur at the α+/β- interface ([250]; reviewed by [277]). The particular α- and γ-subunit isoforms exhibit marked effects on recognition and/or efficacy at the benzodiazepine site. Thus, receptors incorporating either α4- or α6-subunits are not recognised by ‘classical’ benzodiazepines, such as flunitrazepam (but see [351]). The trafficking, cell surface expression, internalisation and function of GABA<sub>A</sub> receptors and their subunits are discussed in detail in several recent
reviews [48, 136, 184, 311] but one point worthy of note is that receptors incorporating the γ2 subunit (except when associated with α5) cluster at the postsynaptic membrane (but may distribute dynamically between synaptic and extrasynaptic locations), whereas as those incorporating the d subunit appear to be exclusively extrasynaptic.

**NC-IUPHAR** [14, 232] class the GABA<sub>A</sub> receptors according to their subunit structure, pharmacology and receptor function. Currently, eleven native GABA<sub>A</sub> receptors are classed as conclusively identified (i.e., α1β2γ2, α1β2γ2, α3β2γ2, α4β2γ2, α4β3γ2, α5β2γ2, α6β2γ2, α6β3γ2 and p) with further receptor isoforms occurring with high probability, or only tentatively [232, 231]. It is beyond the scope of this Guide to discuss the pharmacology of individual GABA<sub>A</sub> receptor isoforms in detail; such information can be gleaned in the reviews [14, 91, 164, 169, 140, 273, 212, 232, 231] and [8, 7]. Agents that discriminate between α-subunit isoforms are noted in the table and additional agents that demonstrate selectivity between receptor isoforms, for example via β-subunit selectivity, are indicated in the text below. The distinctive agonist and antagonist pharmacology of p receptors is summarised in the table and additional aspects are reviewed in [354, 46, 141, 219].

Several high-resolution cryo-electron microscopy structures have been described in which the full-length human α1β3γ2L GABA<sub>A</sub> receptor in lipid nanodiscs is bound to the channel-blocker picrotoxin, the competitive antagonist bicuculline, the agonist GABA (γ-aminobutyric acid), and the classical benzodiazepines alprazolam and diazepam [194].

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**Database links**

**GABA<sub>A</sub> receptors**

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**Introduction to GABA<sub>A</sub> receptors**

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**Channels and Subunits**

GABA<sub>A</sub> receptor α1 subunit

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GABA<sub>A</sub> receptor β3 subunit
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