$GABA_A$ (γ-aminobutyric acid)

Overview: The $GABA_A$ receptor is a ligand-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, $5\text{-}HT_3$ and strychnine-sensitive glycine receptors. The receptor exists as a pentamer of 4TM subunits that form an intrinsic anion channel. Sequences of six α, three β, three γ, one δ, three ρ, one ε, one π and one θ $GABA_A$ receptor subunits (Ensembl gene family ID ENSF00000000053) have been reported in mammals (Korpi *et al.*, 2002; Whiting, 2003; Sieghart, 2006; Olsen and Sieghart, 2008; 2009). The π subunit is restricted to reproductive tissue. Alternatively spliced versions of α4 and α6 (both not functional) α5, β2, β3 and γ2 subunits exist. In addition, three ρ subunits, (ρ1–3) function as either homo- or hetero-oligomeric assemblies (Zhang *et al.*, 2001). Receptors formed from ρ subunits, because of their distinctive pharmacology that includes insensitivity to benzodiazepines and barbiturates, have sometimes been termed $GABA_C$ receptors (Zhang, 2001), but they are classified as distinct $GABA_A$ receptors by NC-IUPHAR on the basis of structural and functional criteria (Barnard *et al.*, 1998; Olsen and Sieghart, 2008; 2009). This position is strengthened by the observation that single amino acid mutations can impart some typical features of $GABA_A$ receptor pharmacology upon such receptors (Belelli *et al.*, 1999; Walters *et al.*, 2000). The distinctive agonist and antagonist pharmacology of ρ receptors is summarized in the table, and additional aspects are reviewed by Zhang *et al.* (2001), Johnston *et al.* (2003) and Chebib (2004).

Many $GABA_A$ receptor subtypes contain α, β and γ subunits with the likely stoichiometry 2α.2β.1γ (Korpi *et al.*, 2002; Fritschy and Brünig, 2003). It is thought that the majority of $GABA_A$ receptors harbour a single type of α and β subunit variant. The α1β2γ2 hetero-oligomer constitutes the largest population of $GABA_A$ 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 θ 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 non-desensitizing tonic current that is important for neuronal excitability in response to ambient concentrations of GABA (see Mody and Pearce, 2004; Semyanov *et al.*, 2004; Farrant and Nusser, 2005). The α and β subunits contribute to the GABA binding site, and both the α and γ subunits are required for the benzodiazepine site. 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 recognized by 'classical' benzodiazepines, such as flunitrazepam. A variety of proteins that associate with the large intracellular M3–M4 loop of $GABA_A$ receptor subunits influence the trafficking, cell surface expression, internalization and function of the receptor (Chen and Olsen, 2007).

The classification of $GABA_A$ receptors has been addressed by NC-IUPHAR (Barnard *et al.* 1998; Olsen and Sieghart, 2008). The scheme utilizes subunit structure, pharmacology and receptor function as the basis for classification. Currently, 11 native $GABA_A$ receptors are classed as conclusively identified (i.e. α1β2γ2, α1βγ2, α3βγ2, α4βγ2, α4β2δ, α4β3δ, α5βγ2, α6βγ2, α6β2δ, α6β3δ and ρ) with further receptor isoforms occurring with high probability, or only tentatively (Olsen and Sieghart, 2008; 2009). It is beyond the scope of this supplement to discuss the pharmacology of individual GABA receptor isoforms in detail; such information can be gleaned in the reviews by Barnard *et al.* (1998), Frolund *et al.* (2002), Korpi *et al.* (2002), Krogsgaard-Larsen *et al.* (2002), Johnston (2005), Sieghart (2006), Möhler (2007) and Olsen and Sieghart (2008; 2009). Agents that discriminate between α subunit isoforms are noted in the table, and additional agents that demonstrate selectivity between receptor isoforms are indicated in the text below.

Nomenclature	$GABA_A$
Ensembl Gene family ID	ENSF00000000053
Selective agonists (GABA site)	Muscimol (partial agonist at ρ subunits), isoguvacine (partial agonist at ρ subunits), THIP (gaboxadol; antagonist at ρ subunits), piperidine-4-sulphonic acid (low efficacy at α4 and α6 subunits, antagonist at ρ subunits), isonipecotic acid (α4 and α6 subunit-selective via relatively high efficacy, antagonist at ρ subunits), (±)-*cis*-2-CAMP (ρ subunit-selective), CACA (ρ subunit-selective),
Selective antagonists (GABA site)	Bicuculline (not active at ρ subunits), gabazine (SR95531), TPMPA (ρ subunit-selective), *cis*- and *trans*-3-ACPBuPA (ρ subunit-selective)
Selective agonists (benzodiazepine site)	Diazepam (not α4 or α6 subunits), flunitrazepam (not α4 or α6 subunits), zolpidem, zaleplon and indiplon (α1 subunit-selective via high affinity), ocinaplon (α1 subunit-selective as essentially a full agonist vs. partial agonist at α2, α3 and α5 subunit-containing receptors), L838417 (α2, α3 and α5 subunit-selective as a partial agonist vs. antagonist at α1 subunit-containing receptors), Ro154513 (selective for α4 and α6 subunit-containing receptors as an agonist vs. inverse agonist at α1, α2, α3 and α5 subunit-containing receptors), TP003 (selective for α3 subunit-containing receptors as a high-efficacy partial agonist vs. essentially antagonist activity at α1, α2 and α5 subunit-containing receptors), TPA023 (selective for α2 and α3 subunit-containing receptors as a low-efficacy partial agonist vs. essentially antagonist activity at α1 and α5 subunit-containing receptors)
Selective antagonists (benzodiazepine site)	Flumazenil (low affinity for α4 or α6 subunits and partial agonist), ZK93426, L838417 (α1 subunit-selective via antagonist activity vs. partial agonist at α2, α3 and α5 subunit-subunit-containing receptors)
Inverse agonists (benzodiazepine site)	DMCM, Ro194603, α3IA (α3-selective via higher affinity and greater inverse agonist activity vs. α1, α2 and α5 subunit-containing receptors), L655708 (α5-selective via high affinity), RY024 (α5-selective via high affinity), α5IA (α5-selective vs. α1, α2 and α3 subunit-containing receptors via greater inverse agonist efficacy), Ro4938581 (α5-selective vs. α1, α2 and α3 subunit-containing receptors via higher affinity and greater inverse agonist activity)
Endogenous allosteric modulators	5α-pregnan-3α-ol-20-one (potentiation), tetrahydrodeoxycorticosterone (potentiation), Zn^{2+} (potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a γ subunit reduces inhibitory potency, Krishek *et al.*, 1998), extracellular protons (subunit dependent activity, Krishek *et al.*, 1996)
Channel blockers	Picrotoxin, TBPS
Probes	$[^3H]$muscimol, $[^3H]$gabazine (SR95531)
GABA site benzodiazepine site	$[^3H]$Flunitrazepam (not α4 or α6 subunit), $[^3H]$zolpidem (α1 subunit-selective), $[^3H]$L655708 (α5 subunit-selective), $[^3H]$RY80 (α5 subunit-selective), $[^3H]$Ro154513 [selectively labels α4 and α6 subunit-containing receptors in the presence of a saturating concentration of a 'classical' benzodiazepine (e.g. diazepam)], $[^3H]$CGS8216, $[^{11}C]$flumazenil (PET ligand with low affinity for α4 or α6 subunits), $[^{18}F]$fluoroethylflumazenil (PET ligand)
Anion channel	$[^{35}S]$TBPS

The potency and efficacy of many GABA agonists varies between receptor $GABA_A$ receptor isoforms (Frolund *et al*., 2002; Krogsgaard-Larsen *et al*., 2002). For example, THIP (gaboxadol) is a partial agonist at receptors with the subunit composition α4β3γ2, but elicits currents in excess of those evoked by GABA at the α4β3δ receptor where GABA itself is a low-efficacy agonist (Brown *et al*., 2002; Bianchi and MacDonald, 2003). The presence of the γ subunit within the heterotrimeric complex reduces the potency and efficacy of agonists (Stórustovu and Ebert, 2006). The $GABA_A$ receptor contains distinct allosteric sites that bind barbiturates and endogenous (e.g. 5α-pregnan-3α-ol-20-one) and synthetic (e.g. alphaxalone) neuroactive steroids in a diastereo- or enantio-selective manner (see Belelli and Lambert 2005; Herd *et al*., 2007; Hosie *et al*., 2007; Veleiro and Burton, 2009). Picrotoxinin and TBPS act at an allosteric site within the chloride channel pore to negatively regulate channel activity; negative allosteric regulation by γ-butyrolactone derivatives also involves the picrotoxinin site, whereas positive allosteric regulation by such compounds is proposed to occur at a distinct locus. Many intravenous (e.g. etomidate, propofol) and volatile (e.g. halothane, isoflurane) anaesthetics and alcohols also exert a regulatory influence upon $GABA_A$ receptor activity (Bonin and Orser, 2008). Specific amino acid residues within $GABA_A$ receptor α and β subunits that influence allosteric regulation by anaesthetic and non-anaesthetic compounds have been identified (see Thompson and Wafford, 2001; Hemmings *et al*., 2005; Hosie *et al*., 2007). Photoaffinity labelling of distinct amino acid residues within purified $GABA_A$ receptors by the etomidate derivative, [^{3}H]-azietomidate, has also been demonstrated (Li *et al*., 2006) and this binding subject to positive allosteric regulation by anaesthetic steroids (Li *et al*., 2009). An array of natural products including flavonoid and terpenoid compounds exert varied actions at $GABA_A$ receptors (reviewed in detail by Johnston, 2005)

In addition to the agents listed in the table, modulators of $GABA_A$ receptor activity that exhibit subunit dependent activity include: salicylidene salicylhydrazide [negative allosteric modulator-selective for β1 vs. β2, or β3 subunit-containing receptors (Thompson *et al*., 2004)]; loreclezole, etomidate, tracazolate mefenamic acid, etifoxine, stiripentol [positive allosteric modulators with selectivity for β2/β3 over β1 subunit-containing receptors, see Korpi *et al*. (2002), Fisher (2009)]; tracazolate [intrinsic efficacy, i.e. potentiation, or inhibition, is dependent upon the identity of the γ1–3, δ or ε subunit co-assembed with α1 and β1 subunits (Thompson *et al*., 2002)]; amiloride [selective blockade of receptors containing an α6 subunit (Fisher, 2002); frusemide [selective blockade of receptors containing an α6 subunit co-assembled with β2/β3, but not β1 subunit, see Korpi *et al*. (2002)]; La^{3+} [potentiates responses mediated by α1β3γ2L receptors, weakly inhibits α6β3γ2L receptors and strongly blocks α6β3δ and α4β3δ receptors (Saxena *et al*., 1997; Brown *et al*. (2002)]; ethanol [selectively potentiates responses mediated by α4β3δ and α6β3δ receptors versus receptors in which β2 replaces β3, or γ replaces δ (Wallner *et al*., 2006, but see also Korpi *et al*., 2007)]; DS1 and DS2 [selectively potentiate responses mediated by δ subunit-containing receptors (Wafford *et al*., 2009)]. It should be noted that the apparent selectivity of some positive allosteric modulators [e.g. neurosteroids such as 5α-pregnan-3α-ol-20-one for δ subunit-containing receptors (e.g. α1β3δ)] may be a consequence of the unusually low efficacy of GABA at this receptor isoform (Bianchi and MacDonald, 2003).

Abbreviations: **3-ACPBuPA**, 3-amino-cyclopentenylbutylphosphonic acid; **(±)-*cis*-2-CAMP**, (±)-*cis*-2-aminomethylcyclopropane carboxylic acid; **α3IA**, 6-(4-pyridyl)-5-(4-methoxyphenyl)-3-carbomethoxy-1-methyl-1*H*-pyridin-2-one; **α5IA**, 3-(5-methylisoxazol-3-yl)-6-[(1-methyl-1,2,3-triazol-4-yl)methyloxy]-1,2,4-triazolo[3,4-*a*]phthalazine; **CACA**, *cis*-aminocrotonic acid; **CGS8216**, 2-phenylpyrazolo[4,3-c]quinolin-3(5)-one; **DMCM**, methy-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate; **DS1**, 4-chloro-*N*-[6,8-dibromo-2-(2-thienyl)imidazo[1,2-a]pyridine-3-yl benzamide; **DS2**, 4-chloro-*N*-[2-(2-thienyl)imidazo[1,2-a]pyridine-3-yl benzamide; **L655708**, ethyl(s)-(11,12,13,13a-tetrahydro-7-methoxy-9-oxo)-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate; **L838417**, 7-*tert*-butyl-3-(2,5-difluoro-phenyl)-6-(2-methyl-2*H*-[1,2,4]triazol-3-ylmethoxy)-[1,2,4]triazolo[4,3-b]pyridazine; **Ro154513**, ethyl-8-azido-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4] benzodiazepine-3-carboxylate; **Ro194603**, imidazo[1,5-a]1,4-thienodiazepinone; **Ro4938581**, 3-bromo-10-difluoromethyl-9*H*-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine; **RY024**, *tert*-butyl-8-ethynyl-5,6-dihydro-5-methyl-6-oxo-4H-imidazol[1,5-α][1,4]benzodiazepine-3-carboxylate; **RY80**, ethyl-8-acetylene-5, 6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5a][1, 4]benzodiazepine-3-carboxylate; **SR95531**, 2-(3′-carboxy-2′-propyl)-3-amino-6-*p*-methoxyphenylpyridazinium bromide; **TBPS**, *tert*-butylbicyclophosphorothionate; **TP003**, 4,2′-difluro-5′-[8-fluro-7-(1-hydroxy-1-methylethyl)imidazo[1,2-á]pyridine-3-yl]biphenyl-2-carbonitrile; **TPA023**, 7-(1,1-dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorphenyl)-1,2,4-triazolo[4,3-*b*]pyridazine; **TPMPA**, (1,2,5,6-tetrahydropyridine-4-yl)methylphosphinic acid; **ZK93423**, 6-benzyloxy-4-methoxymethy-β-carboline-3-carboxylate ethyl ester; **ZK93426**, 5-isopropyl-4-methyl-β-carboline-3-carboxylate ethyl ester

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