

# GABA<sub>C</sub> Receptor

## Key References

- Bormann, J., The 'ABC' of GABA receptors., *Trends Pharmacol. Sci.*, **21**, 16-19 (2000).
- Chebib, M., et al., Unsaturated phosphinic analogues of  $\gamma$ -aminobutyric acid as GABA<sub>C</sub> receptor antagonists., *Eur. J. Pharmacol.*, **329**, 223-229 (1997).
- Johnston, G.A.R., et al., GABA<sub>C</sub> receptors as drug targets, *Curr. Drug Targets CNS Neurol. Disord.*, **2**, 260-268 (2003).
- Johnston, G.A.R., Multiplicity of GABA receptors., in *Benzodiazepine/GABA Receptors and Chloride Channels. Recept. Biochem. and Method.*, Vol. 5, eds. Olsen R.W., Venter J.C. pp 57-71 Alan R. Liss, Inc., New York (1986).
- Martinez-Torres, A., et al., Cloning and functional expression of alternative spliced variants of the  $\rho$ 1  $\gamma$ -aminobutyrate receptor., *Proc. Natl. Acad. Sci. USA*, **95**, 4019-4022 (1998).
- Milligan, C.J., et al., Evidence for inhibition mediated by coassembly of GABA<sub>A</sub> and GABA<sub>C</sub> receptor subunits in native central neurons., *J. Neurosci.*, **24**, 9241-9250 (2004).
- Qian, H. and Ripps, H., The GABA<sub>C</sub> receptors of retinal neurons., *Prog. Brain Res.*, **131**, 295-308 (2001).
- Qian, H. and Ripps, H., Response kinetics and pharmacological properties of heteromeric receptors formed by coassembly of GABA  $\rho$ - and  $\gamma$ 2-subunits., *Proc. R. Soc. Series B.*, **266**, 2419-2425 (1999).
- Qian, H., et al., Molecular and pharmacological properties of GABA- $\rho$  subunits from white perch retina., *J. Neurobiol.*, **37**, 305-320 (1998).
- Ragozzino, D., et al., Design and *in vitro* pharmacology of a selective  $\gamma$ -aminobutyric acidC receptor antagonist., *Mol. Pharmacol.*, **50**, 1024-1030 (1996).
- Woodward, R.M., et al., Characterization of bicuculline/baclofen-insensitive ( $\rho$ -like)  $\gamma$ -aminobutyric acid receptors expressed in *Xenopus* oocytes., *Mol. Pharmacol.*, **43**, 609-625 (1993).
- Zhang, D., et al., Structure and function of GABA<sub>C</sub> receptors: a comparison of native versus recombinant receptors., *Trends Pharmacol. Sci.*, **22**, 121-132 (2001).

## Overview

The term GABA<sub>C</sub> receptor was first proposed by Johnston and coworkers in 1986 to describe a bicuculline- and baclofen-insensitive [<sup>3</sup>H]-GABA binding site present on cerebellar membranes. Subsequent work has shown that GABA<sub>C</sub> receptors are ligand-gated chloride channels that are present in many parts of the brain including the superior colliculus, cerebellum, hippocampus, and, most prominently, the retina. Our current knowledge of GABA<sub>C</sub> receptors comes mainly from studies performed in the visual system, particularly on retinal neurons. GABA<sub>C</sub> receptors are highly sensitive to GABA which displays an EC<sub>50</sub> value of ~1  $\mu$ M. Activation of GABA<sub>C</sub> receptors gives rise to sustained responses with slow onset and offset kinetics. The time constants of GABA<sub>C</sub> receptor relaxation are in the order of tens of seconds, which makes them the slowest ligand-gated channels identified to date. The chloride channels gated by GABA<sub>C</sub> receptors exhibit small single channel conductances (a few picosiemens).

GABA<sub>C</sub> receptors are thought to be composed of GABA  $\rho$  (rho) subunits. At least three types of GABA  $\rho$  subunits have now been cloned from retinal cDNA libraries: human  $\rho$ 1 and its shorter alternative spliced forms (D51 and D450); human  $\rho$ 2; and rat  $\rho$ 1-3. Although most of the GABA  $\rho$  subunits could readily form functional homo-oligomeric receptors when expressed in *Xenopus* oocyte or mammalian cell lines, it is believed that the neuronal GABA<sub>C</sub> receptors are most likely formed by hetero-oligomeric GABA  $\rho$  subunits. In addition, recent studies have suggested that some GABA  $\rho$  subunits could co-assemble with GABA<sub>A</sub> receptor  $\gamma$ 2 subunit to form the hetero-oligomeric receptors with distinct properties. Thus, the molecular compositions of

the native GABA<sub>C</sub> receptors are likely more complicated than original thought. In terms of their pharmacology, GABA<sub>C</sub> receptors are not blocked by traditional GABA<sub>A</sub> receptor antagonists, such as bicuculline and SR 95531. Furthermore, they are not modulated by a range of GABA<sub>A</sub> receptor ligands, including benzodiazepines, barbiturates and some neurosteroids. GABA<sub>C</sub> receptors are also insensitive to baclofen, a highly selective GABA<sub>B</sub> receptor agonist, and likewise neither phaclofen nor saclofen, two GABA<sub>B</sub> receptor antagonists, block GABA<sub>C</sub> responses. In contrast, picrotoxin, a chloride channel blocker, has been shown to antagonize GABA<sub>C</sub> receptors. On rat retinal neurons, however, GABA<sub>C</sub> receptors are insensitive to picrotoxin due to a mutation in the GABA  $\rho$ 2 subunit.

The first selective GABA<sub>C</sub> receptor agonist to be described was cis-4-aminocrotonic acid (CACA), although some studies indicate that it may also act on other GABA receptors and GABA transporters. In contrast, certain GABA<sub>A</sub> and GABA<sub>B</sub> receptor agonists act as antagonists at GABA<sub>C</sub> receptors. Among them, imidazole-4-acetic acid (I4AA), a partial agonist at the GABA<sub>A</sub> receptor, has been shown to inhibit GABA<sub>C</sub> receptors on retinal neurons. Furthermore, recent studies have indicated that I4AA can also partially activate certain subtypes of GABA<sub>C</sub> receptor. Therefore, I4AA might be useful to distinguish various forms of GABA<sub>C</sub> receptors. On the other hand, 3-aminopropyl(methyl)phosphonic acid (APMPA), a GABA<sub>B</sub> receptor agonist, acts as a potent antagonist on the GABA<sub>C</sub> receptors. Finally, 1,2,5,6-tetrahydropyridine-4-yl-methylphosphonic acid (TPMPA) has been described as a selective GABA<sub>C</sub> receptor antagonist. Because it is a low affinity, competitive antagonist at GABA<sub>C</sub> receptors,

high concentrations of TPMPA should be used to completely block GABA responses.

# GABA<sub>C</sub> Receptor

<b>CURRENTLY ACCEPTED NAME</b>	GABA <sub>C</sub>
<b>STRUCTURAL INFORMATION</b>	GABA ρ1 subunit 473 aa (human) GABA ρ2 subunit 465 aa (human) GABA ρ3 subunit 464 aa (rat)
<b>AGONIST</b>	GABA ( <b>A2129</b> )
<b>PARTIAL AGONISTS</b>	Isoguvacine ( <b>G002</b> ), Muscimol ( <b>M1523, G019</b> ), CACA ( <b>A201</b> )
<b>ANTAGONISTS</b>	TPMPA ( <b>T200</b> ), 3-APMPA ( <b>A196</b> ), I4AA <sup>a</sup> ( <b>I0375</b> ), Picrotoxin ( <b>P1675</b> )
<b>PARTIAL ANTAGONISTS</b>	THIP (Gaboxadol) ( <b>P9159</b> ), P4S ( <b>P9159</b> )
<b>MODULATORS</b>	Zn <sup>2+</sup> La <sup>3+</sup>
<b>SIGNAL TRANSDUCTION MECHANISM</b>	Cl <sup>-</sup> influx
<b>RADIOLIGAND OF CHOICE</b>	[ <sup>3</sup> H]-Muscimol
<b>TISSUE EXPRESSION</b>	Retina, superior colliculus, hippocampus, cerebellum, lateral geniculate nucleus, amygdala
<b>PHYSIOLOGICAL FUNCTION</b>	Neuronal inhibition
<b>DISEASE RELEVANCE</b>	Not known

## Abbreviations

**3-APMPA:** 3-Aminopropyl-(methyl)phosphinic acid

**CACA:** *cis*-4-Aminocrotonic acid

**I4AA:** Imidazol-4-acetic acid

**P4S:** Piperidine-4-sulphonic acid

**THIP:** 4,5,6,7-Tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol

**TPMPA:** (1,2,5,6-Tetrahydropyridine-4-yl-methyl)phosphinic acid

## FOOTNOTES

<sup>a</sup> I4AA is a partial agonist on some GABA<sub>C</sub> receptors.