

# GABA<sub>C</sub> Receptor

## Key References

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## 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  $\rho 1-3$ . Using both *Xenopus* oocyte and cell line expression systems, it has been shown that these subunits can form homo-oligomeric receptors with physiological and pharmacological properties similar to those observed for GABA<sub>C</sub> receptors. However, detailed comparison of the responses mediated by neuronal GABA<sub>C</sub> receptor and those exhibited by homo-oligomeric GABA  $\rho$  receptors has uncovered several discrepancies. In addition, various GABA  $\rho$

subunits exhibit different expression patterns in the CNS. These results suggest that the neuronal GABA<sub>C</sub> receptors are formed by hetero-oligomeric GABA  $\rho$  subunits, and that diverse forms of GABA<sub>C</sub> receptors exist in the CNS. However, the exact subunit composition of the GABA<sub>C</sub> receptors has yet to be determined.

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 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  $\rho$  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. 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. On the other hand, 3-aminopropyl(methyl)phosphonic acid (APMPA) can be used to inhibit GABA<sub>C</sub> receptors, but it also activates GABA<sub>B</sub> receptors.

# GABA<sub>C</sub> Receptor

<b>CURRENTLY ACCEPTED NAME</b>	GABA <sub>C</sub>
<b>STRUCTURAL INFORMATION</b>	GABA p1 subunit 473 aa (human) GABA p2 subunit 465 aa (human) GABA p3 subunit 464 aa (rat)
<b>AGONIST</b>	GABA ( <a href="#">A 2129</a> )
<b>PARTIAL AGONISTS</b>	Isoguvacine ( <a href="#">G-002</a> ) Muscimol ( <a href="#">M 1523</a> , <a href="#">G-019</a> ) CACA ( <a href="#">A 201</a> )
<b>ANTAGONISTS</b>	TPMPA ( <a href="#">T-200</a> ) 3-APMPA ( <a href="#">A-196</a> ) I4AA ( <a href="#">I 0375</a> ) <sup>a</sup> Picrotoxin ( <a href="#">P 1675</a> )
<b>PARTIAL ANTAGONISTS</b>	THIP (Gaboxadol) ( <a href="#">T-101</a> ) P4S ( <a href="#">P 9159</a> )
<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

## 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.