

GABA_B Receptor

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Overview

The GABA_B receptor was first recognized over 20 years ago, although the selective agonist for the receptor, *p*- β -chloro-phenyl-GABA (baclofen), had already been marketed as an antispastic agent some nine years earlier with little knowledge about its site of action. The receptor on which baclofen acts is coupled via G_i/G_o proteins to calcium and potassium channels as well as adenyl cyclase in neurons and hence is classified as a metabotropic receptor. Synaptic activation of the receptor in many brain regions produces a slow inhibitory postsynaptic potential (ipsp) contrasting with the fast ipsp produced by GABA_A receptor activation. The GABA_B receptor is not only located post-synaptically, but is also present on pre-synaptic terminals where its activation modulates the release of neurotransmitters. This is clearly evident in spinal cord where activation of the receptor on primary afferent terminals appears to be important in the modulation of nociceptive inputs, and on terminals of monosynaptic inputs to motoneurons in the production of muscle relaxation.

The first indication of the structure of the GABA_B receptor emerged in 1997 when Bettler and colleagues identified a large molecular weight (130 kDa), seven transmembrane spanning receptor protein, GABA_{B1}. This was obtained using an expression cloning technique which was dependent on the development of the high affinity radiolabelled iodinated receptor ligand [¹²⁵I]-CGP64213. No sequence homology with other seven transmembrane spanning receptors was observed, although 20% similarity to metabotropic glutamate receptors was noted. A year after this initial discovery, it was realized that GABA_{B1} is not expressed on the surface of cells without the support of a second recep-

tor protein, referred to as GABA_{B2}, which appears to couple to GABA_{B1} at the level of the endoplasmic reticulum in order to facilitate surface expression. GABA_{B2} also has a seven transmembrane spanning motif and links to GABA_{B1} at their intracellular C-terminals. The combination of these two proteins forms a heterodimer that is crucial for full receptor function. However, no GABA binding has been associated with GABA_{B2}, although it appears that this protein may be more than just a 'trafficker' for GABA_{B1}. Numerous isoforms of GABA_{B1} have been described with at least four forms of human GABA_{B1} protein. However, whether different combinations of these isoforms produce different pharmacological characteristics is not known. Even definitive evidence for the existence of subtypes of native GABA_B receptors has yet to be shown, although there are data which support a separation based on neuropharmacological and neurochemical analysis. A variety of proteins that are unrelated to GABA_B receptors, e.g. CREB2, have been shown to independently associate with high affinity to GABA_{B1} and GABA_{B2} proteins, although they fail to produce any receptor functionality.

A variety of agonists and antagonists for the GABA_B receptor have been developed since the selective action of the archetypal agonist, baclofen, was first described. Notably, high as well as low affinity antagonists (nM - μ M affinity), which penetrate the blood brain barrier, have been produced by Froestl and colleagues. However, the potential of any of these compounds as therapeutic agents is still to be fully realized, although basic research studies would suggest that the antagonists may suppress absence epilepsy seizures, improve cognitive impairment and even act as

neuroprotective agents. Clinical trials with SG5742 (previously known as CGP36742) are currently in progress for mild cognitive impairment. The agonist, baclofen has already been shown to possess clinical efficacy as an anti-spasticity agent and may have analgesic properties in certain types of pain such as trigeminal neuralgia.

Recent studies by Urwyler et al. have demonstrated that the GABA_B receptor can be positively modulated in an allosteric manner by CGP7930 and by GS39783. Neither compounds are receptor agonists but they appear to act on the heptahelical region of GABA_{B2} to enhance the action of the receptor agonists, GABA and baclofen.

GABA_B Receptor

CURRENTLY ACCEPTED NAME	GABA _B
STRUCTURAL INFORMATION	GABA _{B1a} 960 aa (rat), 961 aa (human) GABA _{B2} 941 aa (rat), 941 aa (human)
RECEPTOR SELECTIVE AGONISTS	(R)-Baclofen (G013), 3-Aminopropylphosphinic acid, 3-Aminopropylmethylphosphinic acid (A196)
RECEPTOR SELECTIVE ANTAGONISTS	Phaclofen (P118), 2-Hydroxysaclofen (A6566), CGP35348 (C5851), CGP36742, CGP52432, CGP54626, CGP55845, CGP62349, SCH-50911
POSITIVE ALLOSTERIC MODULATORS	CGP7930 (C0862), CGP13501 (C0987), GS 39783 (G5919)
SIGNAL TRANSDUCTION MECHANISMS	G _s (increase cAMP) G _i (cAMP modulation) ↑ K ⁺ (G) ↓ Ca ²⁺ (G)
RADIOLIGANDS OF CHOICE	[³ H]-R-Baclofen, [³ H]-3-Aminopropylphosphinic acid, [³ H]-CGP54626, [³ H]-CGP62349, [¹²⁵ I]-CGP64213, [¹²⁵ I]-CGP71872
TISSUE EXPRESSION	Mammalian CNS - thalamic nuclei, cerebellar molecular layer, cerebral cortex, interpeduncular nucleus, superior colliculus, dorsal horn of spinal cord.
PHYSIOLOGICAL FUNCTION	Mediates slow inhibitory postsynaptic potentials, Auto- and heteroreceptor-mediated inhibition of transmitter release, increases neuronal membrane K ⁺ conductance, inhibition of membrane Ca ²⁺ conductance, inhibition of adenylyl cyclase, stimulation of MAPkinase.
DISEASE RELEVANCE	Baclofen is used clinically in the treatment of spasticity, pain (when given intrathecally) and intractable cough. Preclinical studies suggest other potential clinical uses for GABA _B agonists (suppression of drug craving, control of oesophageal sphincter function) and GABA _B antagonists (decrease in cognitive impairment, reduction in absence seizures).

Abbreviations

CGP7930: 2,6-Di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol
CGP13501: 3-(3',5'-Di-tert-butyl-4'-hydroxy)phenyl-2,2-dimethylpropanal
CGP35348: 3-Aminopropyl-diethoxymethyl-phosphinic acid
CGP36742: 3-Aminopropyl-n-butyl-phosphinic acid
CGP52432: [3-[[[(3,4-Dichlorophenyl)methyl]amino]propyl]](diethoxy-methyl)phosphinic acid
CGP54626: (3-N[[1-(S)-(3,4-Dichlorophenyl)ethyl]amino-2-(S)-hydroxypropyl]-cyclohexylmethyl)phosphinic acid

CGP55845: (3-N[[1-(S)-(3,4-Dichlorophenyl)ethyl]amino-2-(S)-hydroxypropyl]-benzyl)-phosphinic acid
CGP62349: 3-{1-(R)-[2-(S)-Hydroxy-3-[hydroxy-(4-methoxy-benzyl)-phosphinoyl]-propylamino]-ethyl}-benzoic acid
CGP64213: 3-{1-(R)-[2-(S)-Hydroxy-3-[hydroxy-(5-[3-(4-hydroxy-3-iodo-phenyl)-propionylamino]-pentyl)-phosphinoyl]-propylamino]-ethyl}-benzoic acid
CGP71872: 3-[[1-(R)-(3-[[5-(4-Azido-2-hydroxy-5-iodo-benzoylamino)-pentyl]-hydroxy-phosphinoyl]-2-(S)-hydroxy-propylamino)-ethyl]-benzoic acid
SCH-50911: (+)-(S)-5,5-Dimethylmorpholinyl-2-acetic acid

FOOTNOTES