Introduction

GABA (B) receptors are expressed throughout the nervous system, especially in the brain. They are located both on the postsynaptic membrane alongside the GABA (A) ligand-gated ion channels and in presynaptic membranes, where their activation leads to diminished transmitter release. The latter could be either autoreceptors on the GABA releasing presynaptic terminal or heteroreceptors on neighboring terminals or neurons. GABA (B) receptors on the presynaptic membrane mostly exert their action by releasing the βγ subunits from their G-protein complex, to directly inhibit the typical presynaptic voltage gated Ca2+ channels (Cav2.1 and Cav2.2 or P/Q type and N-type channels), which normally conduct the necessary Ca2+ for synaptic vesicle fusion and transmitter release. This mechanism might serve as a negative feedback on GABA release, controlled by the amount already released (detected by autoreceptors) as well as a part in a synergistic action to inhibit the excitatory signal (detected by heteroreceptors). The latter could be inhibition of glutamate release from a neighboring neuron which is additive to the postsynaptic GABA (A) activation. Another synergistic action of GABA is manifested by the activation of GABA (B) receptors localized on postsynaptic sites. Binding of GABA to these receptors leads to the activation of G-protein activated Inward Rectifier K+ (GIRK or Kir3) channel, hyperpolarization and postsynaptic inhibition.

Molecular Structure of GABA (B) Receptors

The basic functional receptor is a heterodimer composed of two similar subunits each with a seven transmembrane α-helix (7 TM) topology, GABA (B) R1 and GABA (B) R2. Both subunits have a long extracellular N-terminal, are similar in size (961 and 941 amino acids in human for GABA (B) R1 and GABA (B) R2, respectively), share 54% similarity in their amino acid sequence and are dimerized by a coiled coil domain in their intracellular C-termini. However, while GABA (B) R1 binds to agonists and initiates a conformational change in the receptor complex, GABA (B) R2 interacts with and transmits this signal to the intracellular G-protein trimer. In addition to their interaction with G-proteins, which is discussed below, it was recently published that native GABA (B) receptors are in complex with intracellular auxiliary subunits of the KCTD (K+ channel tetramerization domain) protein family. Several members of this protein family were co-immunoprecipitated with GABA (B) R1 and GABA (B) R2 from mouse and rat brain membranes and were shown to influence parameters of GABA (B) signaling (such as agonist potency, receptor desensitization etc.) in an isoform specific manner. This recent finding might explain the variability in native GABA (B) mediated responses, which could not be attributed so far to molecular isoforms, as not many physiologically relevant splice variants of GABA (B) R1 are found. In humans, the two most studied and abundant splice variants are GABA (B) R1a and GABA (B) R1b, which lacks a segment in the N-terminal, giving rise to a shorter extracellular domain (see Figure 1 which summarizes schematically GABA (B) receptors).

Downstream of the Receptor

The most abundant responses to GABA (B) receptor activation are their coupling to G-protein complexes containing a pertussis toxin sensitive Gαq family member and the β and γ subunits which then dissociate from the complex to bind
A) Functional GABA (B) receptors are formed by the interaction of GABA (B) R1 and GABA (B) R2 receptors through coiled-coil motifs in the C-terminus, and through transmembrane and extracellular domains. Ligand binding is achieved through GABA (B) R1 while GABA (B) R2 undergoes allotropic modulation and is responsible for activating the G protein. Two GABA (B) R1 isoforms, GABA (B) R1a and GABA (B) R1b, are expressed in the brain. Two “Sushi motifs” are present GABA (B) R1a and absent in GABA (B) R1b. B) In the hippocampus, GABA (B) receptors are located presynaptically, postsynaptically and on extrasynaptic membranes. On GABA releasing terminals, presynaptic GABA (B) autoreceptors inhibit the release of GABA and heteroreceptors inhibit the release of several other neurotransmitters (glutamate for example). On the postsynaptic membrane, GABA (B) receptors activate K⁺ channels and induce slow inhibitory postsynaptic potentials that inhibit GABA (A) receptor activity. Receptors on extrasynaptic membranes are probably activated by a GABA overflow from nearby synapses. Adapted from reference 5 with permission of Elsevier.
proteins in their vicinity and modulate their function, in part leading to the inhibition of adenylate cyclase, thereby decreasing cAMP levels\(^1,3,9\). \(G_{\text{ip}}\) directly binds to Ca\(_{\text{2.1}}\) and Ca\(_{\text{2.2}}\) channels making them much less responsive to electrical stimulation\(^7\). This molecular event is at the basis of the presynaptic inhibitory action of GABA and is probably due to the clustering of GABA (B) receptors and Ca\(_{\text{2.3}}\) channels in the presynaptic terminal membrane. \(G_{\text{ip}}\) also binds to the \(K_{\text{v}}\)_3 subfamily of \(K^+\) channels, probably to directly gate it open, allowing \(K^+\) efflux and enabling hyperpolarization of the membrane potential\(^8\). The GABA (B)-\(K_{\text{v}}\)_3 system is localized mostly to postsynaptic membranes and its activation maintains a slow synaptic inhibition. GABA (B) was also found to modulate NMDA activation mostly to postsynaptic membranes and its depression or epilepsy\(^3,5,10\).

Induction of a specific form of LTP in specific synapses in the amygdala\(^11\). The contribution of GABA (B) receptors to neuronal activity was also demonstrated in the hippocampus where the inhibitory activity of GABA (B) receptors is dependent on the stimulation frequency and controls the development of GABAergic synapses in this brain region\(^11\).

All these findings nicely demonstrate the important influences on behavior of mammals of a “secondary” GPCR dependent synaptic system, which is used to dynamically and specifically modulate synaptic connectivity and related brain functions.

Alomone Labs offers antibodies to the two GABA (B) Receptors: Anti-GABA (B) R1 (extracellular) (#AGB-001) and Anti-GABA (B) R2 (#AGB-002) antibodies. These antibodies enable the detection of their respective receptors using western blot and immunohistochemistry applications.

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| GABA (B) Receptor Antibodies |
| Anti-GABA (B) R1 (extracellular) | AGB-001 |
| Anti-GABA (B) R2 | AGB-002 |

**Expression of GABA (B) R2 in Mouse Hippocampus.**

**Immunohistochemical staining of mouse hippocampus frozen sections using Anti-GABA (B) R2 antibody (#AGB-002), (1:100).** A. GABA (B) R2 staining (green) is detected in layers including the stratum lacunosum moleculare (SLM) and stratum radiatum of the CA3 layer (star). B. Staining with mouse anti-GAP43 antibody (red) sets apart the SLM. C. Confocal merge suggests the presence of GABA (B) R2 in layers, but not in pyramidal neurons.

**Experimental procedure and figure processed at Alomone Labs.**

Western blot analysis of rat brain membrane:

1. Anti-GABA (B) R2 antibody (#AGB-002), (1:200).
2. Anti-GABA (B) R2 antibody preincubated with the control peptide antigen.

**Experimental procedure and figure processed at Alomone Labs.**

**References**