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Focus on Molecules: The GABA_C Receptor

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1. Structure

γ -aminobutyric acid (GABA), the major inhibitory neurotransmitter in the retina and CNS, exerts its effects by activating three pharmacologically distinct types of GABA receptor (GABA_R), each of which is expressed on retinal neurons. The GABA_CR is a member of the Cys-loop superfamily of ligand-gated ion channels that include the nicotinic acetylcholine, glycine and 5-HT₃ receptors. The pentameric structure of native GABA_C receptors is composed of GABA ρ subunits, and three of which ($\rho 1 - \rho 3$) have been cloned from mammalian retinal cDNA libraries (NCBI accession number for human GABA $\rho 1$, $\rho 2$, and $\rho 3$ subunit: **NM_002042**, **NM_002043**, and **NM_001105580**, respectively). In humans, the $\rho 1$ and $\rho 2$ subunits are located on chromosome 6q15; the $\rho 3$ subunit is on chromosome 3q11. Each of the subunits is capable of forming a GABA-sensitive homooligomeric receptor when expressed in *Xenopus* oocytes, and co-assembly with the γ subunit of the GABA_AR results in the formation of a receptor with functional properties that closely mimic the behavior of GABA_CR on bipolar cells (Qian and Ripps, 1999).

GABA ρ subunits have four transmembrane domains (Fig. 1): a short extracellular loop connects TM II and III, whereas the long intracellular loop that joins TM III and IV is thought to mediate receptor localization, anchoring, and clustering at the neuronal membrane through its interaction with the cytoskeletal protein MAP1b (Hanley et al., 1999). In addition, each ρ subunit contains a very short extracellular C-terminus and an extremely long extracellular N-terminal domain that contains two cystine residues thought to form a disulfide bond. The extracellular domain constitutes the GABA binding site (marked in purple in Fig. 1), formed at the junction between two neighboring subunits. The TM II is located at the innermost side of the receptor, and a cluster of these domains, contributed by five subunits of the pentameric structure, forms the Cl⁻ permeable channel in the center of the receptor (Fig. 1, inset). Although this region exhibits a high degree of homology among all GABA ρ subunits, there is a strikingly consistent difference at the 2' position, i.e., the presence of a proline residue in $\rho 1$ receptors, and a serine residue at the same location in $\rho 2$ receptors. Our earlier studies demonstrated that the amino acid at position 2' of GABA ρ subunits influences response kinetics, receptor pharmacology, and ion selectivity and conductance (Qian et al., 1999).

2. Function

The GABA_CR is expressed predominantly in the retina, although its distribution is also detected in other parts of the CNS. In retina, the GABA_CR is expressed mainly on bipolar cells of every subtype, with extensive distribution in the axon terminal regions and with minor expression in the dendritic region of the cell. Consequently, GABA_CR play an important role in controlling visual signaling from retinal bipolar cells, which link photoreceptors to the amacrine and ganglion cells in the retina.

The inhibitory action of the GABA_CR is mediated by the gated chloride channel. In retinal bipolar cells, there is a high concentration gradient for chloride ions, and opening of chloride channels will clamp the membrane potential of the cell close to the resting potential, increase the membrane conductance, and produce shunting inhibition. The unique physiological properties of the GABA_CR (high GABA sensitivity and slow kinetics of activation and deactivation) indicate that the inhibitory action mediated by this receptor will have a very specific function in the retina. Indeed, the slow response kinetics of GABA_CR-mediated inhibition allows the early phase of the signal to pass the bipolar cell terminal relatively unattenuated, but diminishes the late phase of the response. In other words, inhibition mediated by the GABA_CR at the bipolar cell terminal acts as a high pass filter to make the electrical signal more transient.

In addition to the inhibitory effect mediated by the gated chloride channel, the ρ subunits of the GABA_CR also exhibit metabotropic activity through the interaction of the large intracellular loop with cellular retinoic acid binding protein (CRABP). Since CRABP is a carrier protein that plays important roles in modulating retinoic acid - sensitive gene expression, interaction between the GABA_CR and CRABP provides the link that connects neuronal activity and gene expression in the retina.

3. Disease Involvement

Thus far no disease entities have been directly associated with mutations in the GABA_CR, and GABA_CR knock-out mice do not exhibit observable defects in visual function. Nevertheless, the receptor is clearly a potential target for various ocular disorders because of its key location in the visual pathway. For example, GABA_CR antagonists have been implicated in the prevention of form-deprivation-induced myopia (Stone et al., 2003). Although the molecular machinery is unclear, it is possible that genetic mechanisms involved in the development of myopia are governed in part by the metabotropic activity of the GABA_CR.

The inhibitory action mediated by the gated chloride channel of GABA_CR could also serve as a target to control neurotransmitter (glutamate) release from retinal bipolar cells, and lessen the activity of inner retinal neurons. Reducing the discharge of glutamate and the level of neuronal excitability may serve as a form of therapy for a number of eye diseases. For example, glaucoma, whose clinical hallmark is the loss of retinal ganglion cells, is thought to be caused in large part by glutamate-induced excitotoxicity. In addition, reducing neuronal excitation can diminish metabolic demand in the retina and relieve tissue hypoxia, one of the leading pathogenic factors in several common forms of retinopathy, e.g., diabetic retinopathy, retinopathy of prematurity (ROP), and retinal vasculature occlusions. Thus, reducing neural activity by activating GABA_CR in the retina may prove beneficial for preserving visual function under these pathological conditions.

In summary, a number of unique features that characterize GABA_CR make this type of receptor a particularly suitable target for regulating retinal glutamate level and neuronal activities; (i) The GABA_CR is expressed mainly on the axon terminals of bipolar cells in the mammalian retina, and the GABA_CR-mediated current constitutes a majority of the inhibitory response

of these cells. Activation of the GABA_CR will efficiently reduce the excitatory output of the bipolar cells, i.e., glutamate release to the third order neurons in the retina. (ii) GABA_CR mediate sustained responses with little sign of desensitization. Therefore, activation by externally applied agonists will be able to provide constant inhibition to bipolar cell activity, which will, in turn, reduce excitability for third order neurons in the retina. (iii) The GABA_CR exhibits significantly higher agonist sensitivity, and consequently relatively low drug doses will be required to achieve the desired inhibition of inner retinal neurons. (iv) The restricted distribution of GABA_CR in the CNS minimizes the chances of side effects from local application of GABA_CR agonists.

4. Future Studies

The unique properties of the GABA_CR suggest that it plays a special role in retinal function. Although it has been demonstrated that GABA_CR affect synaptic input from amacrine cells to the bipolar cell terminals in the retina, delineating the exact neuronal circuitry will be an important step in revealing GABA_CR function in visual signal processing. In addition, the study of the metabotropic function of the GABA_CR in retinal neuron is still in its infancy, but could afford a better understanding of the long-term effects of any aberrations in this receptor. The investigation of GABA_CR function will also greatly benefit from the development of GABA_CR-specific agents, which may provide novel therapeutic approaches in treating various eye disorders.

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References

- Hanley JG, Koulen P, Bedford F, Gordon-Weeks PR, Moss SJ. The protein MAP-1B links GABA_C receptors to the cytoskeleton at retinal synapses. *Nature* 1999;397:66–69. [PubMed: 9892354]
- Qian H, Dowling JE, Ripps H. A single amino acid in the second transmembrane domain of GABA ρ subunits is a determinant of the response kinetics of GABA_C receptors. *J. Neurobiol* 1999;40:67–76. [PubMed: 10398072]
- Qian H, Ripps H. Response kinetics and pharmacological properties of heteromeric receptors formed by coassembly of GABA ρ - and γ_2 -subunits. *Proc. R. Soc. Lond. B* 1999;266:2419–2425.
- Stone RA, Liu J, Sugimoto R, Capehart C, Zhu X, Pendrak K. GABA, experimental myopia, and ocular growth in chick. *Invest. Ophthalmol. Vis. Sci* 2003;44:3933–3946. [PubMed: 12939312]

Fig. 1. Structural features of the GABA_C receptor ρ subunit. The extracellular N-terminal domain is derived from a computational model based on the structure of the acetylcholine binding protein; residues in the GABA binding site are drawn in purple. Four transmembrane domains are shown as spirals across the plasma membrane. The large intracellular loop connecting TM III and IV mediates the interactions with other cellular proteins, such as MAP1b and CRABP. Insert. The pentomeric structure illustrates the contribution of the second transmembrane domains of five subunits in forming the Cl⁻ channel.