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GABA$_C$ Receptors in the Vertebrate Retina

Haohua Qian

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Properties of GABA Receptors

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system. The inhibitory action of GABA is mediated by the receptors present on the cell membrane and results in a reduction of neuronal excitability. At least three types of GABA receptors have been characterized. Table 1 summarizes some of the general properties of these three types of GABA receptors. GABA$_A$ receptors are ligand-gated chloride channels. They mediate fast inhibition and have a wide distribution throughout the central nervous system. GABA$_A$ receptors have a diverse molecular composition. At least 16 subunits in six groups have been identified. Pharmacologically, these receptors are antagonized by bicuculline. GABA$_A$ receptors are also the targets of many therapeutic compounds (such as general anaesthetics, sedative drugs, and alcohols). These compounds allosterically modulate GABA$_A$ receptor channel activities. GABA$_B$ receptors belong to the G-protein-coupled receptor superfamily. The inhibition of GABA$_B$ receptors is mediated by indirect gating of either potassium or calcium channels. GABA$_B$ receptors are activated by baclofen and antagonized by phaclofen and saclofen. The subunits of GABA$_B$ receptors have recently been cloned. GABA$_C$ receptors are the newly identified member of the GABA receptor family. They are also linked to chloride channels, with distinct physiological and pharmacological properties. In contrast to the fast and transient responses elicited from GABA$_A$ receptors, GABA$_C$ receptors mediate slow and sustained responses. Pharmacologically, GABA$_C$ receptors are bicuculline- and baclofen-insensitive and are not modulated by many GABA$_A$ receptor modulators (such as benzodiazepines and barbiturates). GABA ρ subunits are thought to participate in forming GABA$_C$ receptors on the neuronal membrane, but the exact molecular composition of these receptors is yet to be determined. GABA$_C$ receptors are expressed in many brain regions, with prominent distributions on retinal neurons, suggesting that these receptors play important roles in retinal signal processing.

Table 1. Characteristics of GABA receptors.

	GABA$_A$ receptor	GABA$_B$ receptor	GABA$_C$ receptor
Category	Ligand-gated channel	G-protein-coupled receptor	Ligand-gated channel
Subunits	α, β, γ, δ, ε, π	GBR1, GBR2	ρ
Agonists	Muscimol, THIP	Baclofen	
Antagonists	Bicuculline, picrotoxin	Phaclofen	TPMPA, picrotoxin
Desensitization	Yes	No	No

Table 1 continued from previous page.

	$GABA_A$ receptor	$GABA_B$ receptor	$GABA_C$ receptor
Modulator	Benzodiazepine barbiturates		Zinc

$GABA_C$ Responses on Retinal Neurons

The term "$GABA_C$ receptor" was first used by Johnston to describe a novel GABA binding site on neuronal membranes (1, 2). Although recent studies indicate a wide distribution of $GABA_C$ receptors in many parts of the central nervous system (3-7), these receptors are most prominently expressed in the vertebrate retina. In the fish white perch retina, rod-driven (H4) horizontal cells were the first retinal neurons where $GABA_C$ receptors were characterized (8). Subsequently, $GABA_C$ receptor-mediated responses have been detected in many types of retinal neurons, including bipolar cells (9-15), cone-driven horizontal cells in catfish (16, 17), cone photoreceptors (18), and ganglion cells (19). Among all these retinal neurons, the rod-driven horizontal cells of white perch are the only cells where GABA responses are mediated solely by $GABA_C$ receptors. The GABA responses elicited from other cells are usually a mixture of GABA receptors and/or GABA transporters. The unique properties of the white perch rod-driven horizontal cell provided an excellent model to characterize the physiological and pharmacological properties of $GABA_C$ receptors on retinal neurons (8, 20).

An example of a solitary rod-driven horizontal cell isolated from white perch retina is shown in Fig. 1, together with a typical GABA-elicited response from such a cell. These horizontal cells receive input from rod photoreceptors in the retina; and when isolated, they keep their typical morphology in culture. Rod-driven horizontal cells have a flat cell body with diameter of 50-100 µm. There are several thick primary dendrites from which many fine processes extend. As shown in Fig. 1, GABA elicits a slow and sustained response from these cells. The GABA-induced membrane currents are mediated by chloride ions and, therefore, exhibit inhibitory actions on these neurons. The responses showed no sign of desensitization, i.e., the responses are maintained at a steady level as long as GABA is present. Furthermore, the GABA responses elicited from these horizontal cells exhibit slow kinetics, which could best be observed in the offset response. After the termination of GABA application, the membrane current returns to the baseline very slowly, with a time constant of ~15 seconds. Such slow and sustained response properties are typical of $GABA_C$ receptors.

It is interesting to note that the neurons in distal retina (i.e., photoreceptors, horizontal cells, and bipolar cells) do not produce action potentials at all. They only generate slow graded responses to light stimuli. It has always been thought that retinal neurons must have special ways to process and analyze such slow signals compared with fast transient neurons of the brain. The kinetics of $GABA_C$ receptor-mediated responses are thus particularly suited for the generatation of signals in distal retinal neurons.

Pharmacology of $GABA_C$ Receptors

$GABA_C$ receptors exhibit a distinct pharmacology that differs from classical $GABA_A$ or $GABA_B$ receptors. $GABA_C$ receptors were first described by Johnston for bicuculline- and baclofen-insensitive GABA binding sites on neuronal membranes (1, 2). More detailed studies indicated that $GABA_C$ receptors on retinal neurons are not sensitive to the competitive antagonists of either $GABA_A$ receptors (such as SR95531 and hydrastine) or $GABA_B$ receptors (such as phaclofen and saclofen). Because the competitive antagonists are thought to interact with the GABA binding sites on the receptors, these results indicate that a different conformation of GABA molecule is preferred for binding to the $GABA_C$ receptor. In agreement with such a notion, the specific agonists of $GABA_A$ and $GABA_B$ receptors exhibit quite different activity on $GABA_C$ receptors. They either have no effect (isonipecotic acid, baclofen), act as partial agonists (isoguvacine, muscimol), or as antagonists (THIP, P4S, 3-APA, and 3-APMPA) (20, 21). I4AA, a partial agonist of $GABA_A$ receptors, behaves as a potent antagonist on

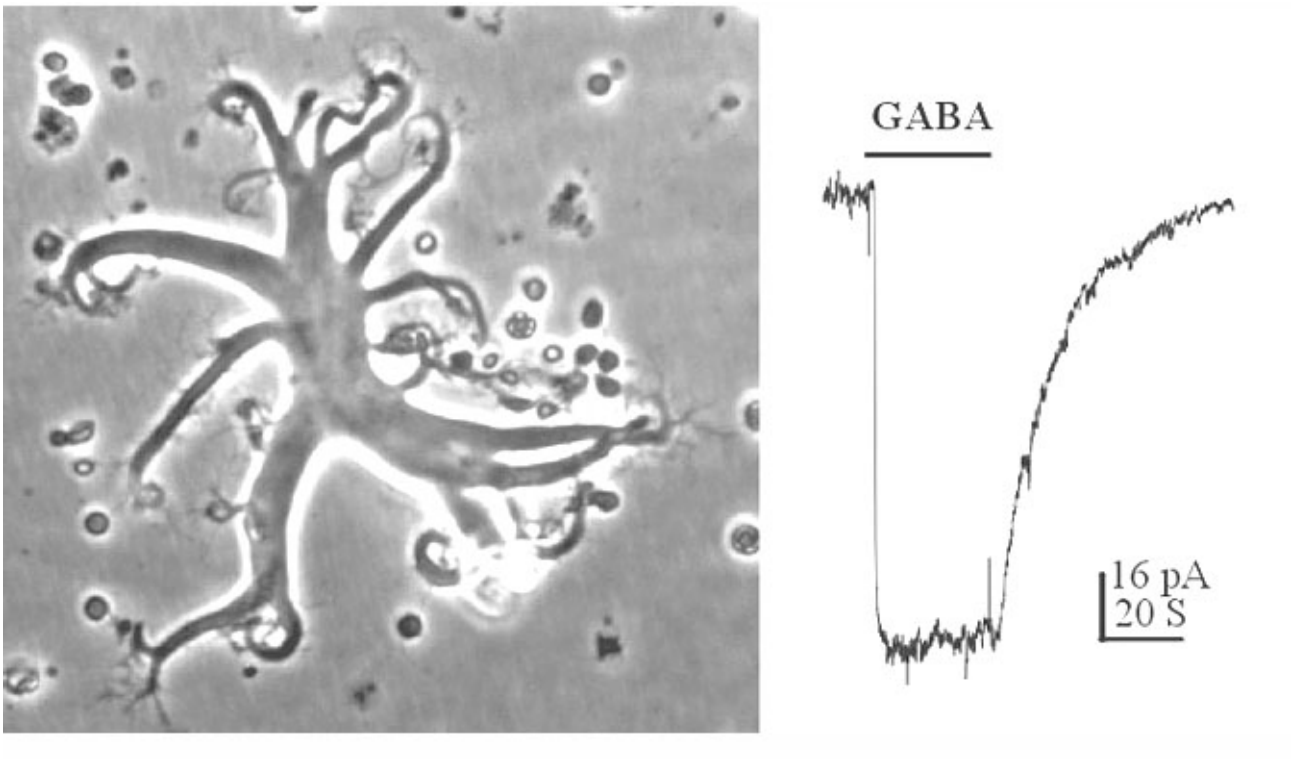

Figure 1. An example of a rod-driven (H4) horizontal cell (left) isolated from white perch retina. GABA elicits a sustained and slow response (right) from these cells mediated by GABA$_C$ receptors. Thus far, this is the only preparation in which the GABA response is mediated solely by GABA$_C$ receptors.

GABA$_C$ responses of retinal neurons and as a partial agonist on expressed GABA$_C$ receptors in *Xenopus* oocytes (20, 22).

GABA$_C$ receptors also differ from classical GABA$_A$ receptors in terms of their responses to various modulators. Two groups of compounds, benzodiazepine and barbiturates, are well-known to modulate GABA$_A$ activity. On the other hand, none of these compounds have any significant influence on responses mediated by GABA$_C$ receptors (23). For example, the GABA-elicited response on white perch rod-driven horizontal cells are virtually identical in the presence or absence of either diazepam or pentobarbital (8). Another class of GABA$_A$ receptor modulators, known as neuroactive steroids, has different effects on the expressed GABA$_C$ receptor in *Xenopus* oocytes. Whereas some of them modulate GABA responses on these receptors, others do not (24, 25). The effect of these neuroactive steroids on GABA$_C$ receptors on neurons has yet to be determined.

Although both GABA$_A$ and GABA$_C$ receptors are linked to chloride channels, the channel properties of these two receptors are quite different. Unlike GABA$_A$ receptors, picrotoxin inhibition on GABA$_C$ receptors in white perch horizontal cells exhibits both competitive and non-competitive mechanisms (20). In mammalian retina (rat), on the other hand, GABA$_C$ receptors are insensitive to picrotoxin blockage (9, 13). The unusual features of GABA$_C$ receptors in rat retina are attributed to a single amino acid substitution in the receptor subunit (26). Furthermore, TBPS (like picrotoxin, another chloride channel blocker on GABA$_A$ receptors) does not block the responses mediated by GABA$_C$ receptors (20, 27). In addition, GABA$_C$ receptor-gated chloride channels exhibit a very small single channel conductance (14, 28).

GABA$_C$ receptor activities are modulated by divalent cations (17, 29-31). In particular, GABA$_C$ receptor-mediated responses are inhibited by low concentrations of zinc ions. The high sensitivity of GABA$_C$ receptors to zinc inhibition is attributed to a histidine residue on the extracellular domain of the subunits (32).

Recently, a new $GABA_C$ receptor antagonist, TPMPA, has become available commercially. This compound is thought to be a specific inhibitor of the $GABA_C$ receptor (33). The availability of such a drug will greatly facilitate further studies of this receptor.

Molecular Biology of $GABA_C$ Receptors

The $GABA_C$ receptor is a member of the ligand-gated channel superfamily. By analogy to the well-studied nicotinic acytocholine receptors, $GABA_C$ receptors are thought to exhibit the structure shown schematically in Fig. 2. These receptors are pentamers, i.e., five subunits constitute the functional channel (34). The receptors have a long extracellular domain containing ligand binding sites and several modulatory sites. In the middle of the receptor, GABA gates an ionic channel. Binding of GABA to the receptor induces a conformational change in receptor structure, which leads to the opening of the channel.

For each subunit forming the receptor, the structure is thought to be that shown in Fig. 3. The subunit contains a long extracellular N-terminal domain that has ligand binding sites, four transmembrane domains, and a large intracellular loop that connects the third and the fourth transmembrane domains. The ionic channel is formed by the second transmembrane domain of each subunit. For the large intracellular loop, there are several putative phosphorylation sites, indicated as colored circles with letter "P" in the figure. Phosphorylation of these residues is implicated for modulation of receptor activities. For example, it has been reported that dopamine modulates $GABA_C$ receptor activity in both catfish cone-driven horizontal cells and tiger salamander bipolar cell terminals (35, 36). On rat bipolar cells, the $GABA_C$ receptor activities are modulated by protein kinase C (37). The modulation of receptor activities by intracellular second messenger systems is also observed at $GABA_C$ receptors expressed on *Xenopus* oocytes (38). However, the mechanisms for modulation by intracellular second messager systems are yet to be determined. Recently, Filippova and coauthors (39) provided evidence for $GABA_C$ receptor internalization upon phosphorylation of the subunits. In addition, there is evidence that the large intracellular loop of $GABA_C$ receptor subunits is involved in the interaction of receptor protein with other intracellular proteins, which may play an important role in the clustering of the receptors on neuronal membranes (40).

There is much evidence to indicate that $GABA_C$ receptors are composed of GABA ρ subunits. These were first cloned from a human retinal cDNA library (41, 42). When expressed in *Xenopus* oocytes, GABA ρ subunits formed functional homo-oligomeric receptors with properties similar to those of $GABA_C$ receptors in retinal neurons (43). Furthermore, the expression of GABA ρ subunits has been detected on retinal neurons where $GABA_C$ receptor-mediated responses have been recorded (44-46). In white perch retina, we have now cloned five forms of GABA ρ subunits (22, 46). Fig. 4 shows a comparison of white perch GABA ρ subunits and those cloned from mammalian retinas. The distances between the various connecting elements represent the degree of divergence among subunits. Unlike the mammalian retina, where only one form of ρ1 and ρ2 subunits has been identified, in white perch there are two forms of the subunit for each ρ1 and ρ2 family. In accordance with their deduced amino acid sequences and the properties of the receptors they formed on *Xenopus* oocytes, each ρ1 and ρ2 family was subdivided into A and B forms. All white perch GABA ρ1 and ρ2 subunits are able to form functional homo-oligomeric receptors when expressed in *Xenopus* oocytes. GABA-elicited responses in these expressed receptors are sustained, bicuculline insensitive, and are not modulated by either benzodiazepines or barbiturates, features typical of $GABA_C$ receptors. Similar to $GABA_C$ receptors on retinal neurons, GABA ρ receptors also gate chloride channels. However, the receptors expressed by each of the GABA ρ subunits display unique response properties that distinguish one from the other. For example, the sensitivity of GABA activation and picrotoxin inhibition varies among subunits. In addition, I4AA acts as an antagonist on A-type ρ receptors, whereas it is a partial agonist on B-type ρ receptors (22).

The waveform of receptor-mediated responses plays an important role in shaping the neuronal signal. Interestingly, the kinetics of the GABA response are also different for the receptors formed by each individual subunits. Current-trace responses to application of 10 μM GABA are illustrated in Fig. 5. These recordings

indicate that there are significant differences in the kinetics of the GABA responses from *Xenopus* oocytes, depending on which white perch GABA ρ subunitis are expressed. To quantitate the kinetics of the GABA response, the offset GABA responses (current traces after GABA application is terminated) were replotted on a semi-logarithmic scale, with the amplitudes normalized to their initial values (Fig. 6). In each case, the data were fit by a straight line, indicating that offset responses can be described by a single exponential function. The slope of the line represents the time constant of the decay and shows that the receptors formed by the various ρ subunits exhibit significant differences in their response kinetics. The average time constants of offset responses elicited from receptors formed by various white perch GABA ρ subunits are shown in the bar graph in Fig. 6C. There are consistent differences between the response kinetics of the two receptor families and between their subgroups. For example, the responses from ρ1 receptors were significantly slower than those of ρ2 receptors. Such difference in the response kinetics among ρ1 and ρ2 receptors are determined, in large part, by a single residue at the second transmembrane domain of the subunits (47). This dichotomy among ρ1 and ρ2 subunits is well conserved in all species where GABA ρ subunits have been cloned. ρ1 subunits, which have a proline at the residue site, combine to make a receptor with slower kinetics, whereas ρ2 subunits, which contain a serine at the residue site, form receptors with faster response rate. Thus, receptors made of human ρ1 subunits exhibit slower response kinetics than receptors made of ρ2 subunits (5). The kinetic differences among the receptors formed by various GABA ρ subunits could provide building blocks for the nevous system to construct different types of signal filters and different types of neuronal signaling in the nervous system.

Function of GABA$_C$ Receptors in the Retina

Although rod-driven horizontal cells provide an excellent model in which to characterize GABA$_C$ receptors in the retina, recent studies indicate that GABA$_C$ receptors are present on various other types of retinal neurons. GABA$_C$ receptor-mediated responses have been recorded from cone-driven horizontal cells in catfish (16, 17), cone photoreceptors (18), and some types of ganglion cells (19). GABA$_C$ responses are particularly prominent in bipolar cells of every species examined thus far (9-12, 14, 15), and both immunocytochemistry and *in situ* hybridization studies indicate that GABA$_C$ receptors are present on bipolar cells (15, 44, 45, 48). It appears that these receptors play an important role in shaping signal transmission from bipolar cells to third-order neurons in the retina.

Fig. 7 illustrates some examples of bipolar cells isolated from white perch retina. These bipolar cells keep their morphology when isolated in culture. They usually have a pear-shaped cell body from which several dendrites and one axon extend. The GABA responses of bipolar cells in white perch retina have both transient and sustained components, indicating both GABA$_A$ and GABA$_C$ receptors are present, as shown in Fig. 8. The transient component can be selectively blocked by the co-application of bicuculline, leaving a more sustained response. Thus, the electrophysiological and pharmacological properties of GABA$_C$ receptors on bipolar cells are very similar to those of GABA$_C$ receptors on rod-driven horizontal cells (11, 14, 37, 49).

Different kinetic properties of GABA$_A$ and GABAc receptors suggest that they play different roles in mediating inhibition on bipolar cell terminals (15, 46, 50). Furthermore, various subtypes of bipolar cells exhibit different proportions of GABA$_A$ and GABA$_C$ receptors. For example, in the rat retina, there is a clear difference in the contribution of GABA$_A$ and GABA$_C$ receptors to rod and cone bipolar cells (51). In white perch, too, different morphological types of bipolar cells exhibit different proportions of GABA$_C$ receptor-mediated components (14). These results strongly suggest that different subtypes of bipolar cell use various mixtures of GABA$_A$ and GABA$_C$ receptors to perform different activities and help create the variety of functional pathways through the retina.

Because of the presence of multiple GABA receptors on retinal neurons, it is sometimes difficult to isolate the contributions of each receptor. Recent studies on ganglion cell responses reveal some interesting features of GABA$_C$ receptors in retinal information processing. For example, activation of GABA$_C$ receptors leads to more

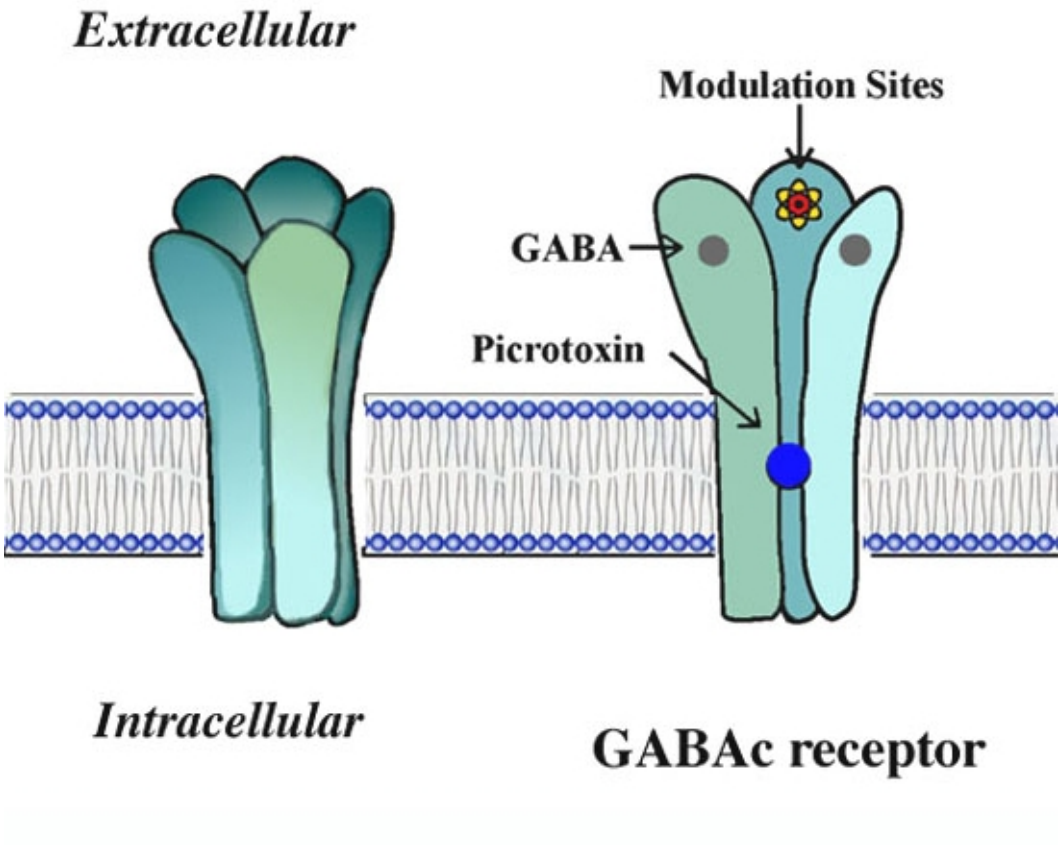

Figure 2. Schematic diagram of $GABA_C$ receptors. These receptors are formed by five subunits with an ionic channel in the middle of the receptor. On the extracellular side, the receptor contains the binding site for GABA and several modulatory sites.

transient light responses in ganglion cells (52) and the delayed inhibition mediated by $GABA_C$ receptors is thought to play a major role in shaping edge-enhancement of ganglion cell receptive fields (53). The bipolar cell to ganglion cell synapse is probably heavily influenced by inhibitory amacrine feed-forward or feedback synapses, and these appear to be via primarily $GABA_C$ receptors.

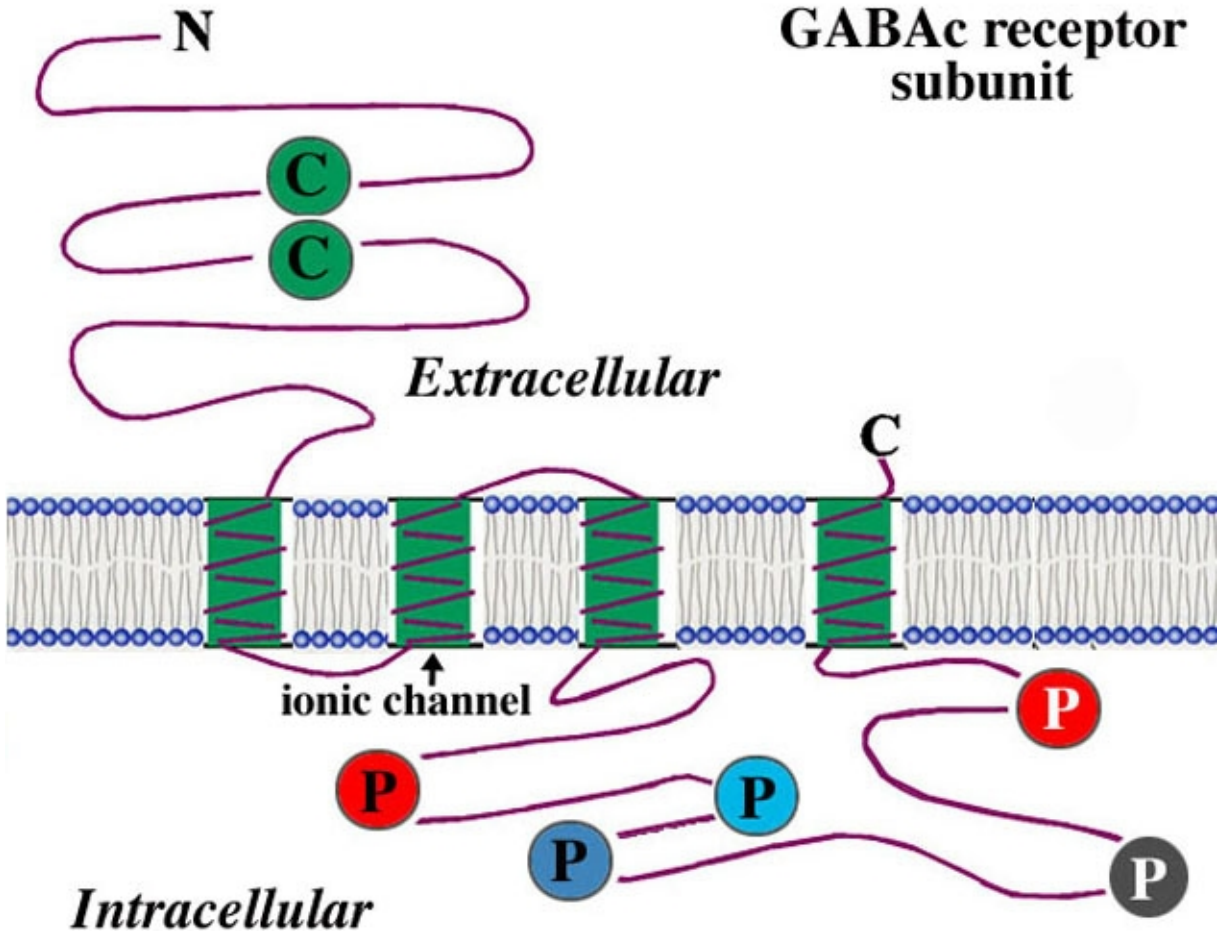

Figure 3. Schematic digram of the GABA$_C$ receptor subunits. Each subunit contains a long extracellular N-terminal region that contains two cystine residues thought to form disulfide bonds. The extracellular domain forms the GABA binding sites and other modulatory sites. The subunit crosses the cell membrane four times with a short C-terminal region on the outside of the cell. The second transmembrane domain forms the ionic channel of the receptor. There are several putative phosphorylation sites on the large intracellular loop between the third and the fourth transmembrane domains (colored circles with letter "P").

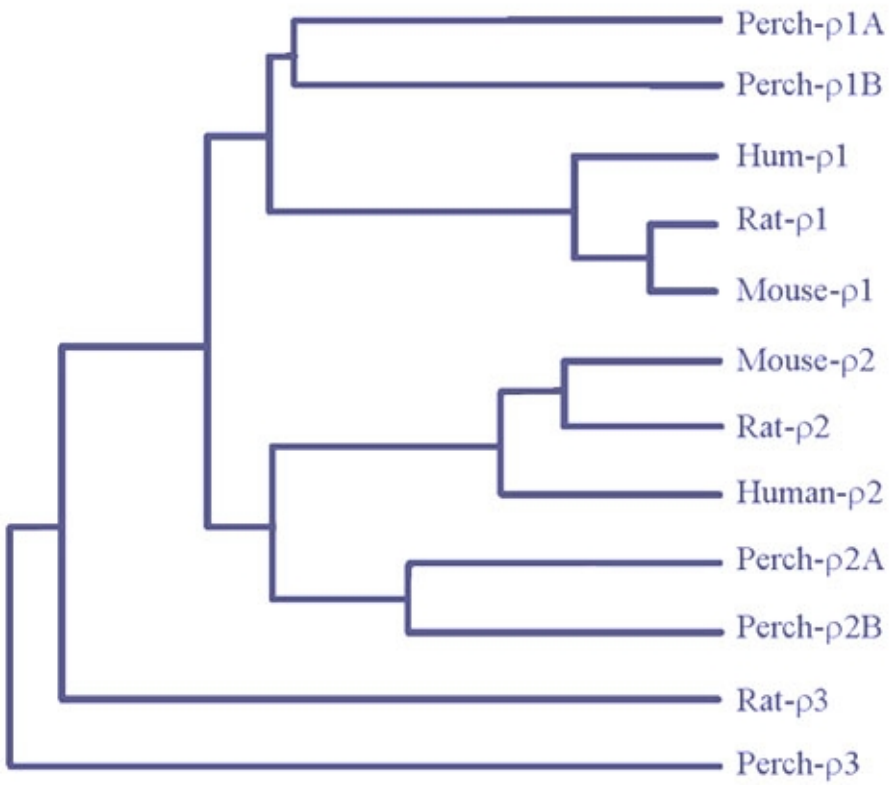

Figure 4. Dendrogram showing the relation of the GABA ρ subunits cloned from white perch retina to those cloned from mammalian retinas. Analysis was performed on the deduced amino acid sequence of each subunit.

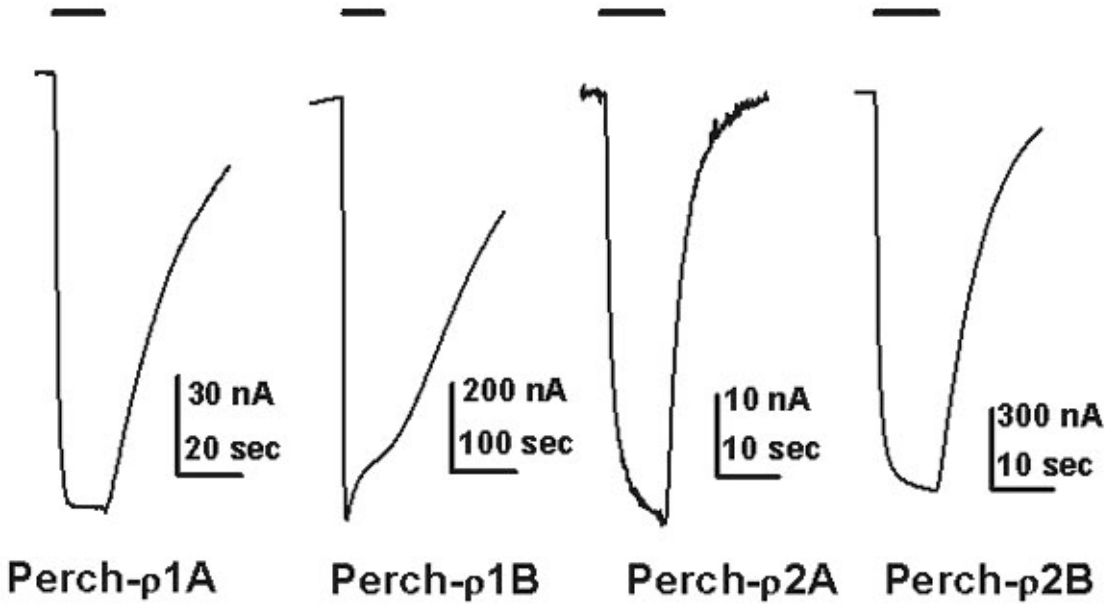

Figure 5. GABA (10 μM) induced responses from white perch GABA ρ subunits expressed in *Xenopus* oocytes. The duration of GABA application is shown by the bar above each trace. Variations in response amplitude often result from the different level of receptor expression in individual oocytes; response kinetics are a relatively stable feature, independent of amplitude.

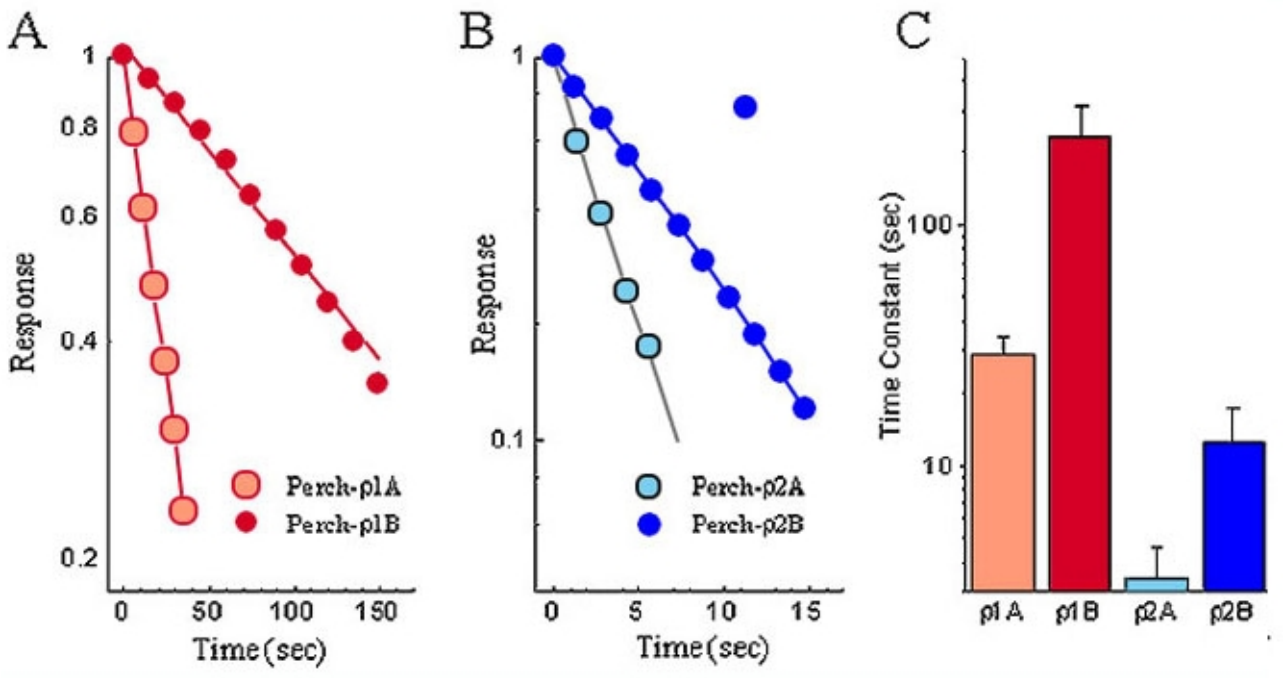

Figure 6. Kinetics of the GABA responses obtained from the white perch GABA ρ receptors expressed in *Xenopus* oocytes. A. Semi-logarithmic plot of GABA responses measured at various times following the offset of drug application (10 μM GABA); the responses were normalized to their initial amplitude at the time of offset. The responses are well fit by straight lines, indicating that the relationship can be described by a single exponential function. B. A similar analysis applied to the offset GABA responses obtained from perch ρ2 receptors. Note different time scales in A and B. C. Comparison of the time constants calculated from GABA offset responses elicited from various GABA ρ receptors.

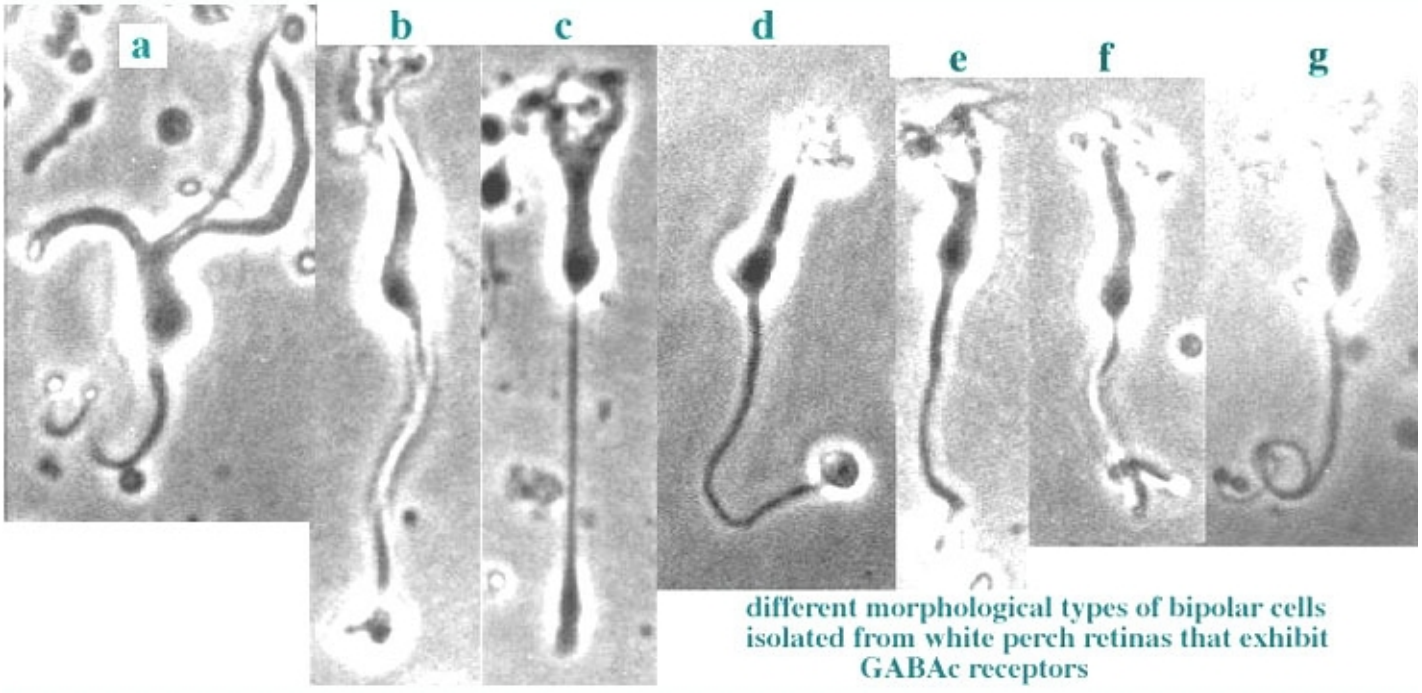

Figure 7. Examples of solitary white perch bipolar cells in culture.

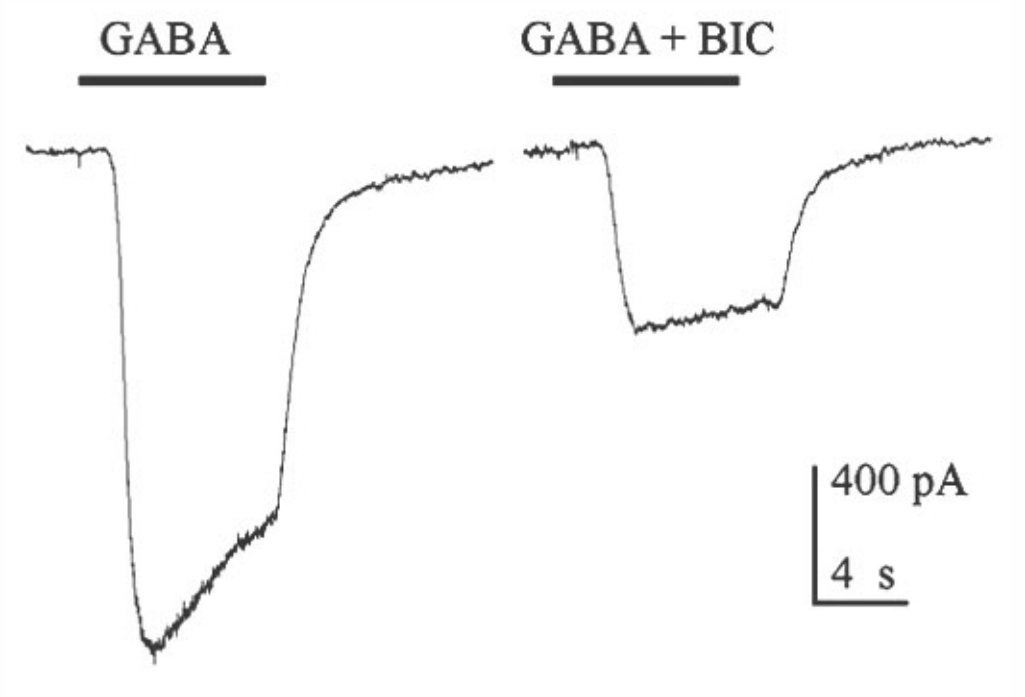

Figure 8. GABA-elicited responses from isolated white perch bipolar cells. The membrane currents elicited by GABA application (left) contain both transient and sustained components, indicating both $GABA_A$ and $GABA_C$ receptors are present. In the pesence of bicuculline, $GABA_A$ receptor activity is inhibited, revealing sustained GABA responses mediated by $GABA_C$ receptors (right).

About the Author

Dr. Haohua Qian was born in Jiangsu, China. He received his B.A. in Biology from Nanjing University (1982), M.S. in Neurobiology from Shanghai Institute of Physiology (1985), and Ph.D. in Anatomy and Cell Biology from University of Illinois at Chicago (1991). He is currently an Assistant Professor of Neurosciences in the Department of Ophthalmology and Visual Sciences at the University of Illinois at Chicago. During his postdoctoral studies with Dr. John E. Dowling at Harvard University, he characterized a new type of GABA receptor, the $GABA_C$ ρ receptor, on retinal neurons. He is currently continuing these studies on the molecular structure and physiological functions of $GABA_C$ receptors in the vertebrate retina.

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