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Physiological and Pharmacological Characterization of Glutamate and GABA Receptors in the Retina

Xiong-Li Yang, Ying Shen[1], Ming-Hu Han, and Tao Lu

Shanghai Institute of Physiology and Key Laboratory of Neurobiology, Chinese Academy of Sciences, Shanghai 200031; [1]Graduate student of Department of Biological Science and Technology, Zhejiang University, Hangzhou, 310027, China

Glutamate and γ-aminobutyric acid (GABA) are major excitatory and inhibitory neurotransmitters in the vertebrate retina, respectively. Using the whole-cell patch clamp technique and a rapid solution changer, glutamate and GABA receptors have been extensively investigated in carp retina. Glutamate receptors on both horizontal and amacrine cells may be an AMPA preferring subtype, which predominantly consists of flop splice variants. $GABA_A$ and $GABA_C$ receptors coexist in bipolar cells and they both show significant desensitization. Kinetics analysis demonstrated that activation, deactivation and desensitization of the $GABA_C$ receptor-mediated response of these cells are overall slower than those of the $GABA_A$ response. Endogenous modulator Zn^{2+} in the retina was found to differentially modulate the kinetic characteristics of the $GABA_C$ and $GABA_A$ responses.

Key Words: Retina, Glutamate, γ-aminobutyric acid, Desensitization, Receptor, Patch-clamp

There are a variety of neurotransmitters in the retina, among which glutamate and γ-aminobutyric acid (GABA) are major excitatory and inhibitory neurotransmitters, respectively. Photoreceptors and bipolar cells located on the direct pathway of visual signal both release glutamate as neurotransmitters, whereas GABA released by most horizontal and amacrine cells mediates lateral interaction (Fig. 1). In this article we present some of the results obtained in our laboratory concerning glutamate receptors on horizontal and amacrine cells and GABA receptors on bipolar cells in carp retina.

GLUTAMATE RECEPTORS OF HORIZONTAL CELLS

Photoreceptors (cones and rods) release glutamate as the neurotransmitter. Since horizontal cells are the second-order neurons receiving signal from photo-

Corresponding to: Xiong-Li Yang, Shanghai Institute of Physiology and Key Laboratory of Neurobiology, Chinese Academy of Sciences, Shanghai 200031, China

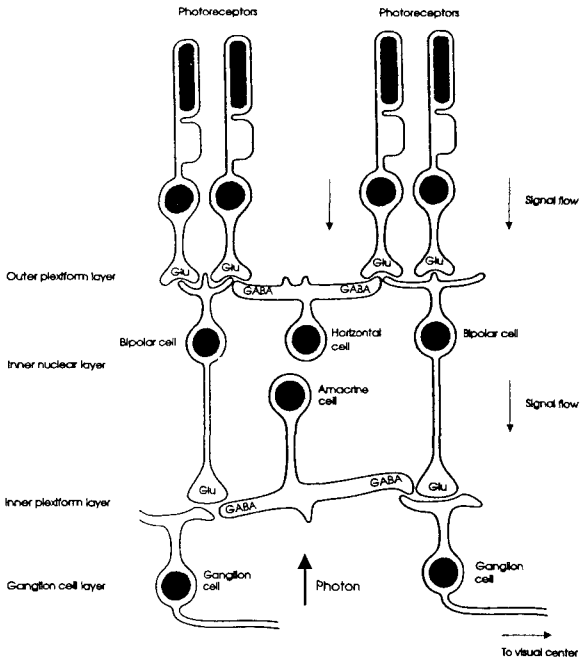

Fig. 1. Schematic diagram of the retinal neuronal circuitry. Glutamate is the major neurotransmitter of photoreceptors and bipolar cells; GABA is the neurotransmitter of horizontal and amacrine cells. Adapted from Barnstable (1993).

receptors, it was of interest to characterize glutamate receptors on these cells. Actually, *in situ* hybridization experiments, using cDNA or mRNA oligonucleoctide as the probe, have shown abundant expression of some genes of the glutamate receptor family in horizontal cells (Hughes et al, 1992; Hamassaki-Britto et al, 1993).

Recent evidence has suggested that there are at least five subtypes of glutamate receptors, which are named after their specific agonists: kainate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA), L-AP4 and trans-1-aminocyclopentane-1,3-dicarboxylic acid (tACPD) receptors. The first three receptors are known to cause depolarization in post-synaptic cells. The L-AP4 receptor appears to be autoreceptor which self-regulates the release of neurotransmitter. The ACPD receptor is believed to be involved in activating inositol phosphate (IP) metabolism (Hollmann & Heinemann, 1994).

Glutamate depolarizes horizontal cells, which is in association with a suppression of their light responses. Actions of the above glutamate receptor agonists on horizontal cells are different. In most cases, L-AP4 and NMDA receptors failed to induce any responses from horizontal cells, while the actions of kainate and AMPA on both membrane potential and light responses mimicked those of glutamate. These actions persisted even after the release of neurotransmitter from pre-synaptic terminals was blocked by cobalt ions, suggesting that they did act on horizontal cells, but not on presynaptic cells (Yang & Wu, 1991a). Furthermore, kainate- and AMPA-induced depolarization of horizontal cells could be completely blocked by CNQX, a specific antagonist of non-NMDA receptors (Yang & Wu, 1991a; Wilson, 1994). All these results indicate that there exist AMPA/KA receptors on horizontal cells.

Patch clamp technique has provided a powerful tool for identifying glutamate receptors in isolated horizontal cells. Using the whole-cell configuration of patch clamp technique, in combination with a rapid solution changer, we found in isolated horizontal cells that the current responses induced by glutamate and AMPA were very similar and showed significant and rapid desensitization (Fig. 2a and 2b). That is, the currents rapidly sagged to a steady state of much lower level in amplitude (equilibrium state) soon after they reached a peak value. The time constant of desensitization was less than 2 ms. In contrast, the responses induced by kainate were invariably sustained and no desensitization could be observed (Fig. 2c). We have determined the values of EC_{50} (the concentration of ligand producing half-maximal response) for glutamate- and AMPA-induced peak current as about 1 mM, nearly 7-fold higher than that for kainate (Lu et al, 1998). These results are consistent with the pharmacological characteristics of AMPA receptors, suggesting that the glutamate receptor on horizontal cells may be an AMPA preferring subtype.

A selective AMPA receptor antagonist, GYKI 53655, has been recently developed (Lerma et al, 1997). It was found in our experiments that GYKI

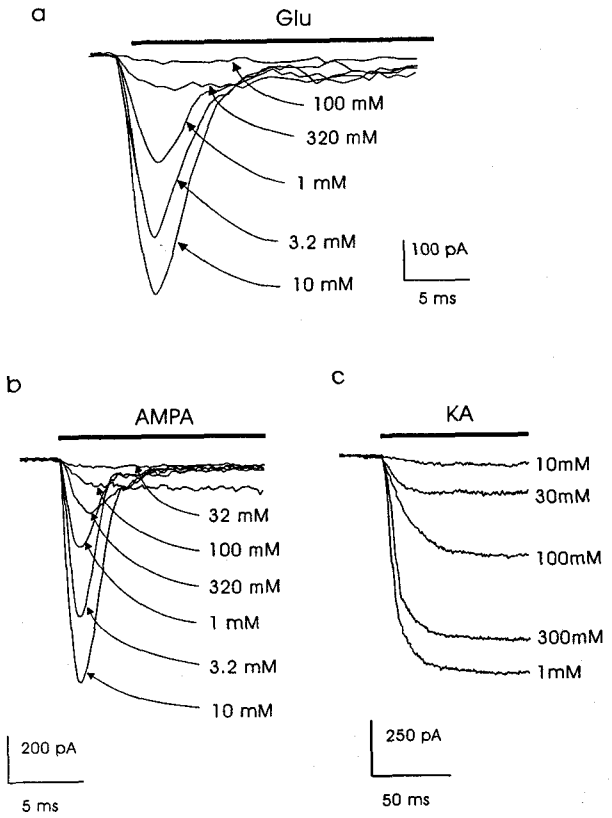

Fig. 2. Responses of H1 cells to various concentrations of glutamate receptor agonists. (a, b, c) responses from three different H1 cells to various concentrations of glutamate (Glu), AMPA and kainate (KA), respectively. Note that the responses to glutamate and AMPA, but not to kainate, usually show striking desensitization. With the application of glutamate and AMPA, peak currents steadily increased with increasing concentrations of these agonists (indicated by arrows), while the equilibrium currents did not. Durations of drug application are indicated by the horizontal bars above each set of responses. Adapted from Lu et al. (1998).

53655 completely blocked glutamate-induced currents in horizontal cells at a very low concentration (10 μM, Fig. 3a and 3b), further strengthening the notion that horizontal cells may exclusively express the AMPA subtype of glutamate receptors (Lu et al, 1998).

Desensitization is a ubiquitous characteristics of ligand-gated channels. Microscopically, desensitization is thought as a process in which receptors enter a deactivation state from the resting or open state (Jones & Westbrook, 1996). Much evidence have revealed that there exist two alternative splice variants named flip and flop, which are generated by the gene splicing in RNA editing (Sommer et al, 1990). The two splice variants are much different in physiological properties (Mosbacher et al, 1994; Partin et al, 1996). In native and recombinant receptors, it was reported that differences in proportion of flip/flop variants at AMPA receptors may result in different rates and extents of desensitization (Sommer et al, 1990). In expressed glutamate receptors, some desensitization modulators have been found to differentially modulate flip and flop receptors and thus used to identify splice variants composing glutamate receptors (Partin et al, 1994; Johansen et al, 1995; Sekiguchi et al, 1997). Therefore, we examined the effects of desensitization modulators, concanavalin A (Con A), cyclothiazide (CTZ), aniracetam and 4-[2-(phenylanlfonylamino) ethylthio]-2,6-difluoro-pheynoxy acetamide (PEPA), on AMPA receptors-mediated responses in horizontal cells (Shen et al, 1999a). Incubation of Con A suppressed the peak response but weakly potentiated the equilibrium response of horizontal cells to glutamate. CTZ blocked glutamate-induced desensitization in a dose-dependent manner, which resulted in a steady increase of the equilibrium current and shifted the dose-response relationship of the equilibrium current to the right, but slightly suppressed the kainate-induced sustained current. In reference to the results obtained in *Xenopus* oocytes, HEK cells and other neurons (Partin et al, 1993; Wong & Mayer, 1993), these effects of Con A and CTZ not only further demonstrated that glutamate receptors expressed in carp horizontal cells may be an AMPA preferring subtype, but also led us to speculate that these receptors may predominantly carry the flop splice variants. This speculation was further supported by the actions of aniracetam and PEPA, both flop-preferring modulators of AMPA receptors (Johansen et al, 1995; Sekiguchi et al, 1997), on glutamate-induced responses of horizontal cells. It was found that these chemicals considerably blocked desensitization of glutamate-induced currents in horizontal cells in a dose-dependent manner, but only slightly potentiated kainate-induced currents. Fig. 3c shows how the response of horizontal cell to 1 mM glutamate was potentiated by PEPA of increasing concentrations. For comparison, potentiation-dose relationships for aniracetam and PEPA are shown in Fig. 3d. It was evident that PEPA was 1,000 fold more potent than aniracetam at these receptors (Shen et al, 1999a). These experiments all suggest that the AMPA receptor on

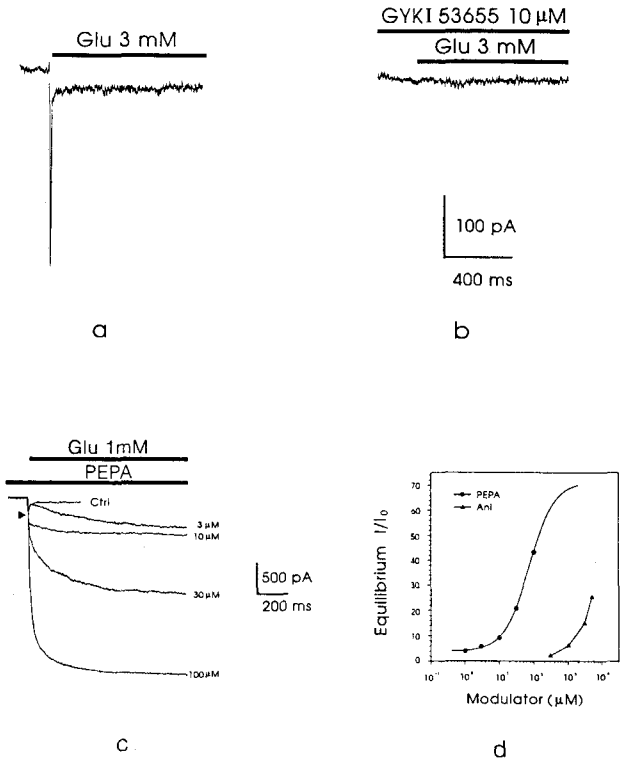

Fig. 3. Glutamate (Glu)-induced currents in horizontal cells and their modulation. (a) Response of an horizontal cell to application of 3 mM glutamate, showing significant desensitization. (b) In the continuous presence of 10 μM GYKI 53655, glutamate failed to induce any response from the same cell. (c) Responses of another horizontal cell to 1mM glutamate in the presence of PEPA of increasing concentrations. Control (Ctrl) peak response is marked by a triangle. (d) PEPA (circle) and aniracetam (triangle) dose-response relationships for modulation of 1 mM glutamate-induced responses. Ordinate is fold potentiation given as the equilibrium current (I) induced by co-application of PEPA and glutamate/the corresponding response (I_0) recorded without PEPA. Adapted from Lu et al. (1998) and Shen et al. (1999a).

carp horizontal cells may be predominantly assembled from flop splice variants.

Whether alternative splice variants may be related to some specialized functions of AMPA receptors is still unclear. Transmitter release is discontinuous in most central spike-producing neurons. In contrast, neurons responding with graded-potentials release transmitter continuously and their synaptic vesicles fuse with the presynaptic membrane at a high rate. Accordingly, it has been demonstrated that these neurons possess distinct morphological features at their synapses (for instance, the electron-dense ribbon in the presynaptic terminal) (Eliasof & Werblin, 1993). It is feasible that there should be receptor characteristics at the postsynaptic neurons to match the graded and continuous transmitter release. Since photoreceptors release glutamate continuously in the dark, rapid desensitization of glutamate receptors in horizontal cells appears to be one of the mechanisms that prevent horizontal cells from the toxic effects caused by the accumulation of glutamate. (Another mechanism may be the uptake of glutamate by photoreceptors and Müller cells) (Eliasof & Werblin, 1993). In addition, it was indeed found in isolated retinas that CTZ could significantly change the light responsiveness of horizontal cells, suggesting that desensitization may play an important role in modulating the light sensitivity of these cells.

GLUTAMATE RECEPTORS OF AMACRINE CELLS

In the inner retina amacrine cells receive glutamatergic synaptic input from bipolar cells (Dowling, 1987). Morphological evidence indicates the expression of glutamate receptors in amacrine cells (Hamassaki-Britto et al, 1993; Brandstätter et al, 1994; Koulen et al, 1996; Brandstätter et al, 1998). In addition, depolarizing responses of amacrine cells to glutamate receptor agonists were demonstrated electrophysiologically (Dixon & Copenhagen, 1992; Zhou & Fain, 1995). Our analysis of glutamate receptors of carp amacrine cells (Shen et al, 1999a) yielded results similar to those obtained with horizontal cells.

Whole-cell inward membrane currents induced from carp amacrine cells by glutamate showed significant desensitization. In contrast, kainate invariably induced sustained currents from these cells. GYKI 53655 completely blocked the response of amacrine cells to 10 mM glutamate, suggesting that amacrine cells may predominantly express AMPA receptors.

PEPA and CTZ were used to study the splice variant composition of amacrine cells. CTZ potentiated both the glutamate peak and equilibrium currents and potentiation caused by 100 μM CTZ was nearly 10 fold increase over control values. 100 μM PEPA, however, produced a nearly a 50-fold increase of the glutamate response. It was recently reported that a comparison of the actions of PEPA versus CTZ (P/C ratio) facilitates the detection of the splice variant heterogeneity (Sekiguchi et al, 1998). The P/C ratio for the glutamate equilibrium current of the amacrine cells is high (4.39) (see Fig. 4), which suggests that these cells carry the flop splice variants (Shen et al, 1999b).

GABA RECEPTORS OF BIPOLAR CELLS

Recently the study of GABA receptors has made important progress in revealing a novel $GABA_C$ receptor, in addition to common $GABA_A$ and $GABA_B$ receptor subtypes. Like the $GABA_A$ subtype, this novel subtype consists of chloride channels, but is insensitive to the specific $GABA_A$ receptor antagonist bicuculline (BIC) and $GABA_B$ agonist baclofen (Lu-

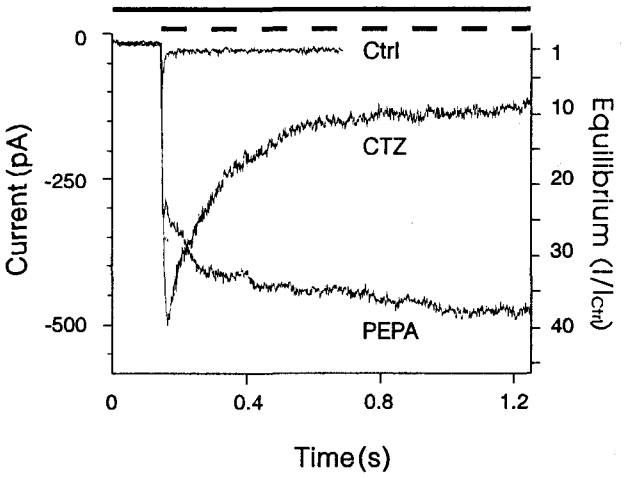

Fig. 4. Comparison of potentiation of 3 mM glutamate-induced currents (Ctrl) by 30 mM cyclothiazide (CTZ) and PEPA from a single amacrine cell. Duration of drug application is indicated by the horizontal bars above the responses; dashed for glutamate and solid for modulators. I and I_0 are current amplitudes with or without modulators, respectively. Adapted from Shen et al. (1999b).

kasiewicz, 1996; Cherubini & Strata, 1997). $GABA_C$ receptor is abundant in the visual system, including the retina (Qian & Dowling, 1995; Lukasiewicz, 1996).

Most horizontal and amacrine cells are GABAergic in the retina. Bipolar cells receive feedforward signals from both photoreceptors and horizontal cells in the outer plexiform layer (Yang & Wu, 1991b) and feedback signals from amacrine cells via the reciprocal synapses in the inner plexiform layer (Müller & Marc, 1990). In a recent experiment, we found that GABA suppressed light responses of the color-opponent bipolar cells, which respond to red and green lights with depolarization and hypolarization respectively, with the response driven by input from red cones being invariably suppressed to a greater extent. Both $GABA_A$ and $GABA_C$ receptors on bipolar cells may be involved in this suppression (Zhang & Yang, 1998).

Using the whole-cell configuration of patch-clamp technique, we systematically studied the GABA receptors in carp rod-dominant ON bipolar cells. These cells have an enlarged characteristic axon terminal, which is easily identified under light microscope after enzyme digestion and mechanical trituration (Lu & Yang, 1995).

GABA application induced inward currents with significant desensitization in bipolar cells (Fig. 5a). Local application of GABA to the axon and dendrites of bipolar cells could both induce currents, suggesting that GABA released from both horizontal and amacrine cells may influence these cells. GABA-induced responses was only partially blocked by BIC of 800 μM (Fig. 5b) and the remaining BIC-resistant component was insensitive to baclofen, but dramatically inhibited by the co-application of I4AA, a specific competitive antagonist of $GABA_C$ receptor (Fig. 5c) (Han et al, 1997). These results clearly indicate that both $GABA_A$ and $GABA_C$ receptors co-exist in carp bipolar cells.

A number of authors claimed that $GABA_C$ receptor-mediated responses showed minimal desensitization in contrast to significant desensitization of $GABA_A$ receptor-mediated responses (Feigenspan et al, 1993; Calvo et al, 1994; Qian & Dowling, 1995). It is suggested that $GABA_A$ receptors mediate transient signal, whereas $GABA_C$ receptors are important for mediating sustained signal (Qian & Dowling, 1995; Djamgoz, 1995). However, we found that the $GABA_C$ response induced from carp bipolar cells showed striking desensitization (see Fig. 5b), even at low concentration (3 μM) of GABA (Han et al, 1997), suggesting that the $GABA_C$ receptor may play a role for mediating transient signal as well. Actually, it was found in isolated retina that suppression of transient responses of amacrine cells by GABA could be mediated by $GABA_C$ receptors while suppression of sustained responses could be mediated by $GABA_A$ receptors (Zhang et al, 1999). Existence of the desensitizing $GABA_C$ receptor further suggests that there may exist several subtypes of $GABA_C$ receptors, which may be distinct in intracellular mechanisms and/or subunit composition.

Since GABA receptors modulate neuronal spiking (McDonald & Olsen, 1994), coincidence detection

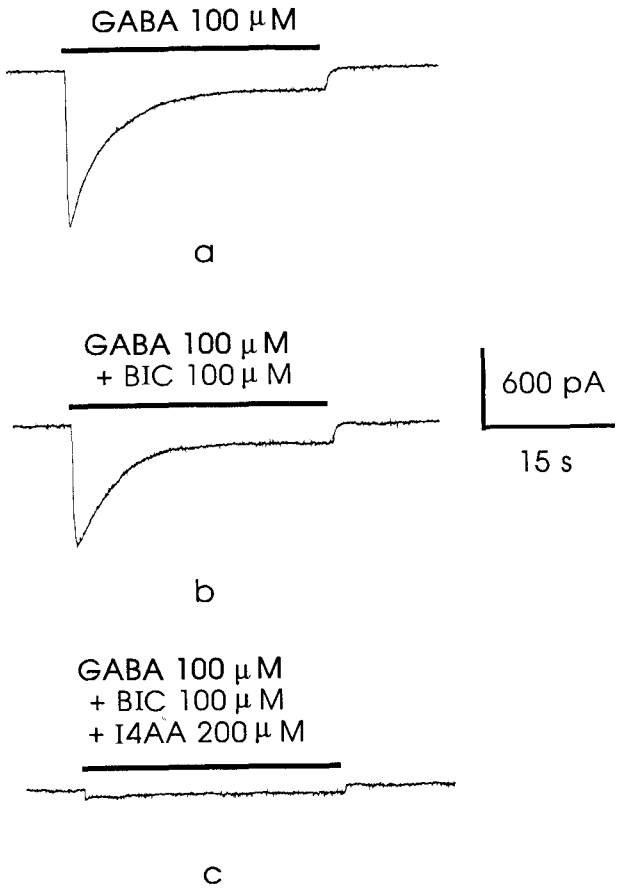

Fig. 5. $GABA_A$ and $GABA_C$ receptor-induced response of a rod-dominant ON bipolar cell. (a) inward current induced by 100 μM GABA. (b) $GABA_C$ receptor-mediated current separated from the response to 100 μM GABA by application of 100 μM bicuculline (BIC). Note that the $GABA_C$ receptor-mediated current showed striking desensitization. (c) the $GABA_C$ current was potently suppressed by 200 μM I4AA. Adapted from Han et al. (1997).

(Konig et al, 1996) and the output of synchronized neuronal circuitry by affecting the inhibitory postsynaptic current (IPSC) (Cobb et al, 1995), it was speculated that the neural activity could be modulated at different levels via influencing the decay and duration of IPSC. Now that $GABA_A$ and $GABA_C$ receptors coexist in bipolar cells, it was of interest to explore the differences in kinetics between these two receptors response kinetics and how the receptor kinetics were modulated. To address these questions is essential for understanding the role of GABA in inhibitory synaptic transmission and its underlying mechanism.

Kinetic characteristics of $GABA_A$ and $GABA_C$ receptors studied in our experiments included activation, desensitization and deactivation. In these experiments, 100 μM BIC and 100 μM I4AA were used to suppress the $GABA_C$ and $GABA_A$ response components respectively, so that the response kinetics of these components could be separately characterized. Step application of GABA allowed us to record the whole course of activation and desensitization of receptors, whereas the recovery of current after pulse application of GABA represented deactivation of receptors (Partin et al, 1996; Han & Yang). Fig. 6 shows activation (a), desensitization (b) and deactivation (c) of both $GABA_C$ and $GABA_A$ receptors of bipolar cells.

Activation kinetics of both $GABA_A$ and $GABA_C$ receptors could be well fitted by monoexponential functions, but the time constant (τ) for the $GABA_C$ component (42.06 ms) was much slower than that for the $GABA_A$ component (9.50 ms). Similarly, although both $GABA_C$ and $GABA_A$ receptors desensitized during continued application of GABA, desensitization of the former was much slower. Moreover, the desensitization of the $GABA_C$ response was well fitted by a monoexponential function, while the decay of the $GABA_A$ response was characterized by a fast and a slow component, suggesting that the mechanism underlying desensitization of the two receptors are different. It was further found that the sum of two (a fast and a slow) exponentials was required to adequately describe deactivation of both the receptors, with the $GABA_C$ being much slower. Overall, the $GABA_C$ receptor was slower in kinetics than the $GABA_A$ receptor on the bipolar cells (Han & Yang).

It was reported that GABA inhibited the Ca^{2+} influx into bipolar cell terminals, which was mediated via $GABA_A$ and $GABA_C$ receptors (Matthews et al, 1994). Activation of $GABA_A$ receptors suppressed the Ca^{2+} influx with fast kinetics and a narrow dynamic range, whereas $GABA_C$ receptors caused inhibition of

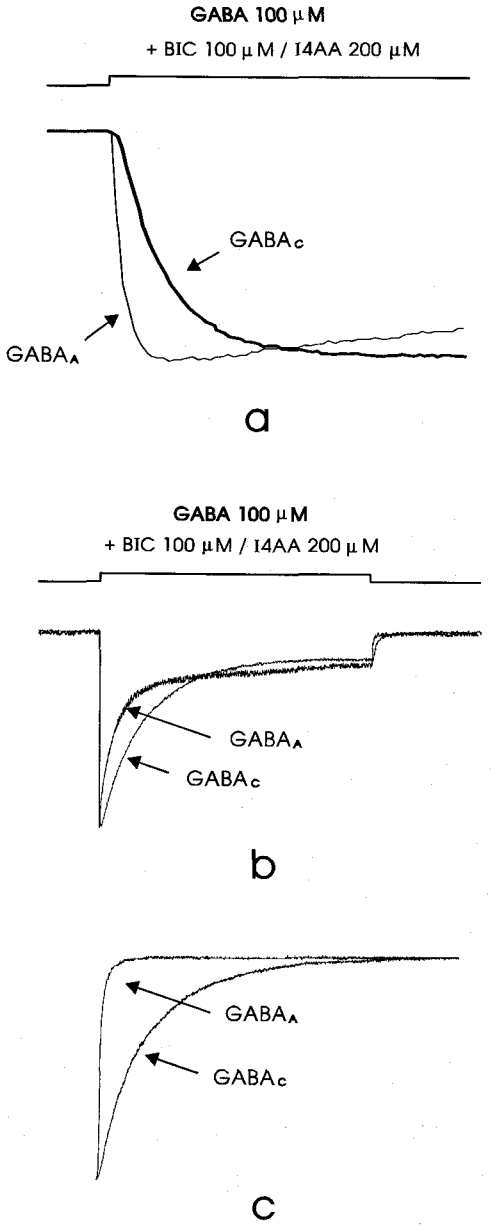

Fig. 6. Comparison of kinetic characteristics of $GABA_C$ and $GABA_A$ receptors on bipolar cells---activation (a), desensitization (b) and deactivation (c). 100 μM bicuculline (BIC) suppressed the $GABA_A$ receptor-mediated component to separate the $GABA_C$-mediated component from the response to 100 μM GABA. 100 μM I4AA suppressed the $GABA_C$ receptor-mediated component to separate $GABA_A$-mediated component from the response to 100 μM GABA. $GABA_A$ and $GABA_C$ responses were both normalized.

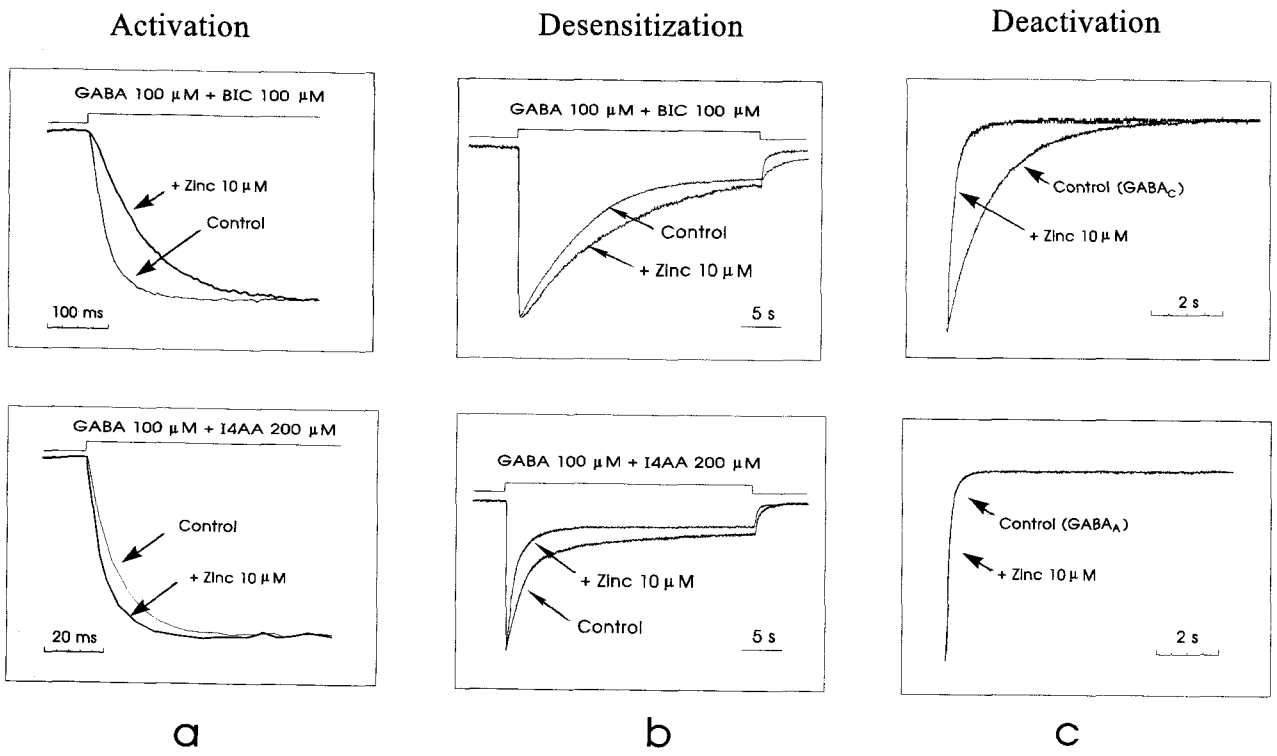

Fig. 7. Differential modulation by zinc of activation (a), desensitization (b) and deactivation (c) of $GABA_C$ and $GABA_A$ responses on bipolar cells. BIC, bicuculline. The effects of 10 μM zinc on the $GABA_C$ and $GABA_A$ responses recorded from a single bipolar cell are shown in upper and lower panels, respectively. For comparison, control and Zn^{2+} responses were normalized. Note the differences in time scales for different panels. Adapted from Han & Yang (1999).

the Ca^{2+} influx with slow onset and a wider dynamic range (Pan & Lipton, 1995). This difference is apparently due to the distinct kinetics of these two receptors. It is intriguing to speculate that the desensitizing $GABA_C$ receptors may be involved in processing relatively slower signals, whereas the $GABA_A$ receptors may mainly participate in relatively faster signal transmission.

Kinetics of $GABA_A$ and $GABA_C$ receptors could be modulated by Zn^{2+}, which has been recently demonstrated to function as an endogenous modulator of ligand- and voltage-gated ion channels in the central nervous system (Harrison & Gibbons, 1994). In the retina it has been shown that Zn^{2+} is abundantly localized near the terminals of photoreceptors, suggesting that Zn^{2+} may probably be released from the synaptic terminals with glutamate and modulates the activity of the second-order neurons. In the salamander retina, it was demonstrated that Zn^{2+} blocked the GABA-induced depolarization in membrane potential of horizontal cells (Wu et al, 1993). In bipolar cells, the $GABA_C$-induced responses are invariably down-regulated in amplitude domain by Zn^{2+} (Qian & Dowling, 1995; Qian et al, 1997). In regard to the modulation of $GABA_A$-induced responses by Zn^{2+} the results now available are inconsistent. Unlike significant potentiation of $GABA_A$ responses by low concentration (0.1 ~ 100 μM) of Zn^{2+} in skate bipolar cells (Qian et al, 1997), we consistently observed suppression of the $GABA_A$ responses by Zn^{2+} on carp bipolar cells (Han & Yang, 1999).

Our recent results further showed that Zn^{2+} exerted differential effects on the kinetics of the $GABA_A$ and $GABA_C$ responses (Fig. 7): it slowed down activation and desensitization of the $GABA_C$ response whereas it accelerated those of the $GABA_A$ response (Fig. 7a and 7b); it accelerated deactivation of the $GABA_C$ response, but had no apparent effect on that of the $GABA_A$ response (Fig. 7c) (Han & Yang, 1999). The differential effects of Zn^{2+} may result from distinct subunit compositions of these receptors. It was reported that recombinant receptors lacking γ subunits were more sensitive to zinc (Harrison & Gibbons, 1994; Berger et al, 1998). Moreover, the homomeric

ρ1 receptors have two Zn^{2+} binding sites: one competitive and one noncompetitive (Chang et al, 1995). It is thus plausible that the events occurring at these two binding sites may result in the different effects of Zn^{2+}.

CONCLUSION

Using the patch-clamp technique, our recent work demonstrates that the glutamate receptors on horizontal and amacrine cells may be an AMPA preferring subtype, which predominately consists of flop splice variants. $GABA_A$ and $GABA_C$ receptors coexist in bipolar cells with the latter showing significant desensitization. Response kinetics (activation, deactivation and desensitization) of $GABA_C$ receptors are overall slower than those of $GABA_A$ receptors. Endogenous modulator zinc exerts differential actions on the kinetics of the $GABA_C$ and $GABA_A$ responses.

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