

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

Xiong-Li Yang, Ying Shen¹, Ming-Hu Han, and Tao Lu

Shanghai Institute of Physiology and Key Laboratory of Neurobiology, Chinese Academy of Sciences, Shanghai 200031; ¹Graduate 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 Zn²⁺ 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-

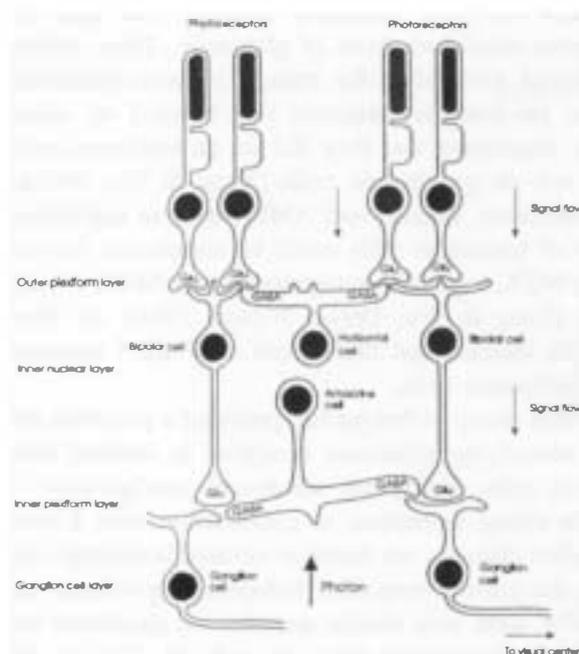


Fig. 1. Schematic diagram of the retinal neuronal circuitry. Glutamate is the major neurotransmitter of photoreceptors and bipolar cells; GABA is the neurotransmitter of horizontal and amacrine cells. Adapted from Barnstable (1993).

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

receptors, it was of interest to characterize glutamate receptors on these cells. Actually, *in situ* hybridization experiments, using cDNA or mRNA oligonucleotide 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

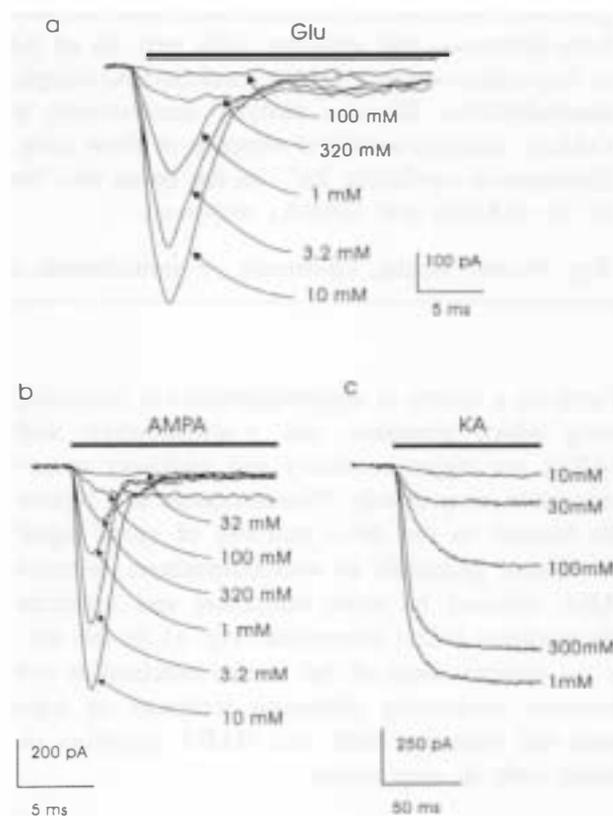


Fig. 2. Responses of H1 cells to various concentrations of glutamate receptor agonists. (a, b, c) responses from three different H1 cells to various concentrations of glutamate (Glu), AMPA and kainate (KA), respectively. Note that the responses to glutamate and AMPA, but not to kainate, usually show 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 ($10 \mu\text{M}$, 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-(phenylamylfonylamino) 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

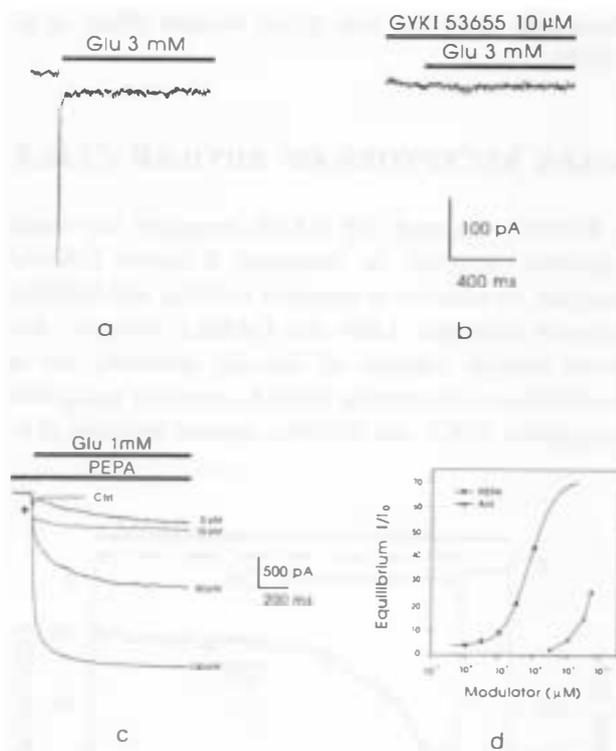


Fig. 3. Glutamate (Glu)-induced currents in horizontal cells and their modulation. (a) Response of an horizontal cell to application of 3 mM glutamate, showing significant desensitization. (b) In the continuous presence of $10 \mu\text{M}$ GYKI 53655, glutamate failed to induce any response from the 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 (Hamasaki-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 μ M CTZ was nearly 10 fold increase over control values. 100 μ M 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-

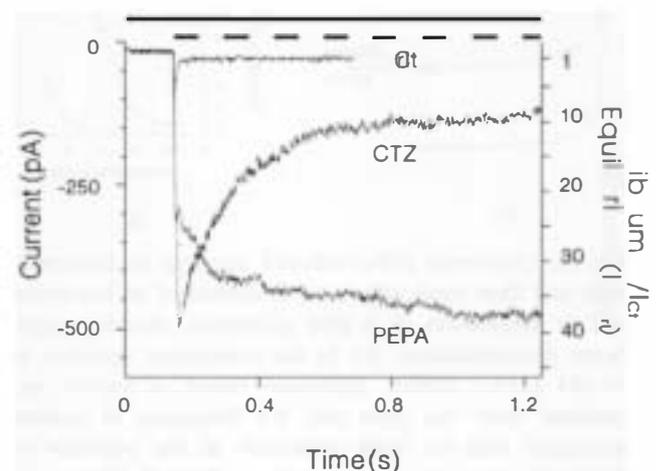


Fig. 4. Comparison of potentiation of 3 mM glutamate-induced currents (Ctrl) by 30 mM cyclothiazide (CTZ) and PEPA from a single amacrine cell. Duration of drug application is indicated by the horizontal bars above the responses; dashed for glutamate and solid for modulators. I_1 and I_0 are current 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 hyperpolarization 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 μ M (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 μ M) of GABA (Han et al, 1997), suggest-

ing 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

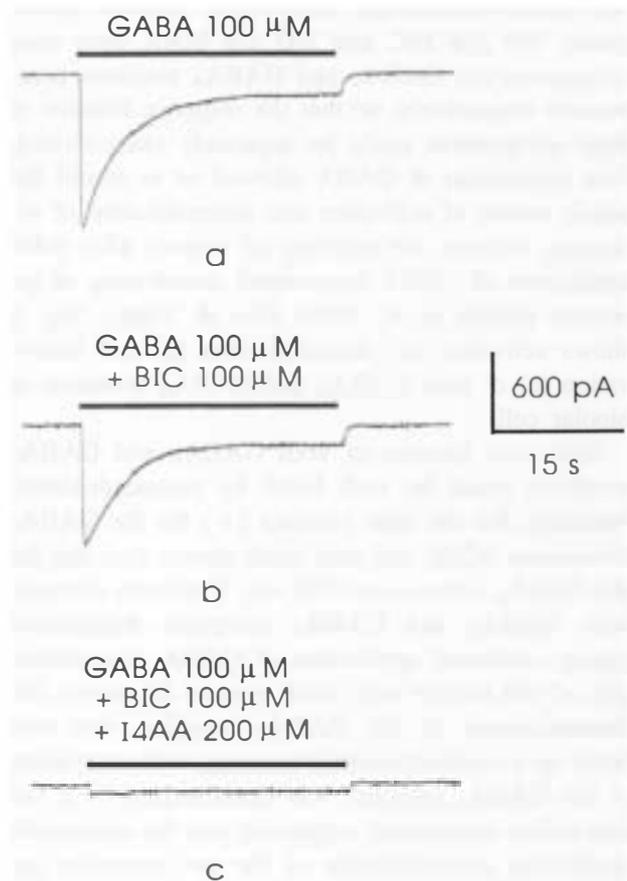


Fig. 5. GABA_A and GABA_C receptor-induced response of a rod-dominant ON bipolar cell. (a) inward current induced by 100 μ M GABA. (b) GABA_C receptor-mediated current separated from the response to 100 μ M GABA by application of 100 μ M bicuculline (BIC). Note that the GABA_C receptor-mediated current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

(Konig et al, 1996) and the output of synchronized neuronal circuitry by affecting the inhibitory post-synaptic 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 μ M BIC and 100 μ M 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 Ca²⁺ 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 Ca²⁺ influx with fast kinetics and a narrow dynamic range, whereas GABA_C receptors caused inhibition of

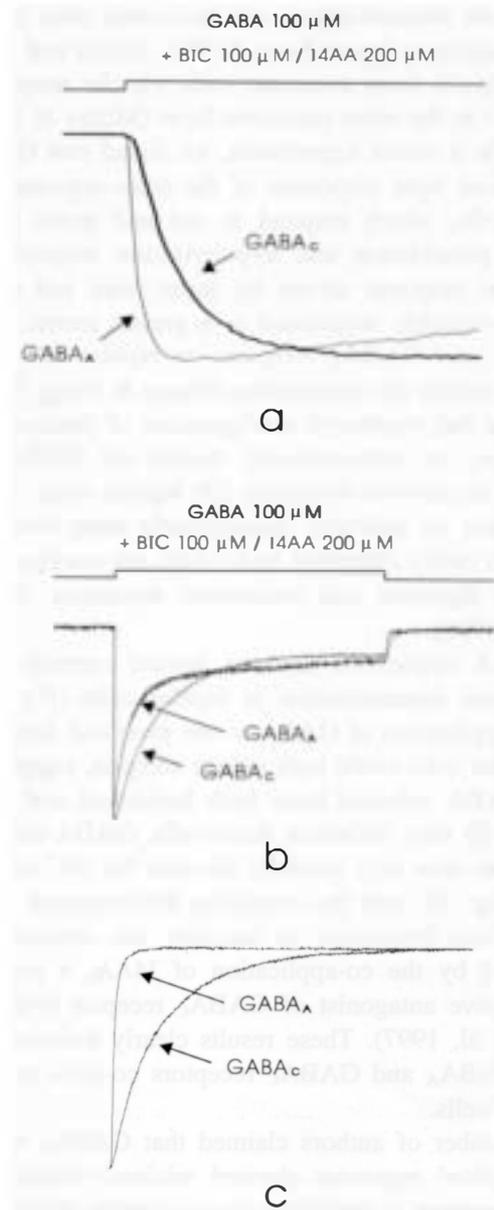


Fig. 6. Comparison of kinetic characteristics of GABA_C and GABA_A receptors on bipolar cells—activation (a), desensitization (b) and deactivation (c). 100 μ M bicuculline (BIC) suppressed the GABA_A receptor-mediated component to separate the GABA_C-mediated component from the response to 100 μ M GABA.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

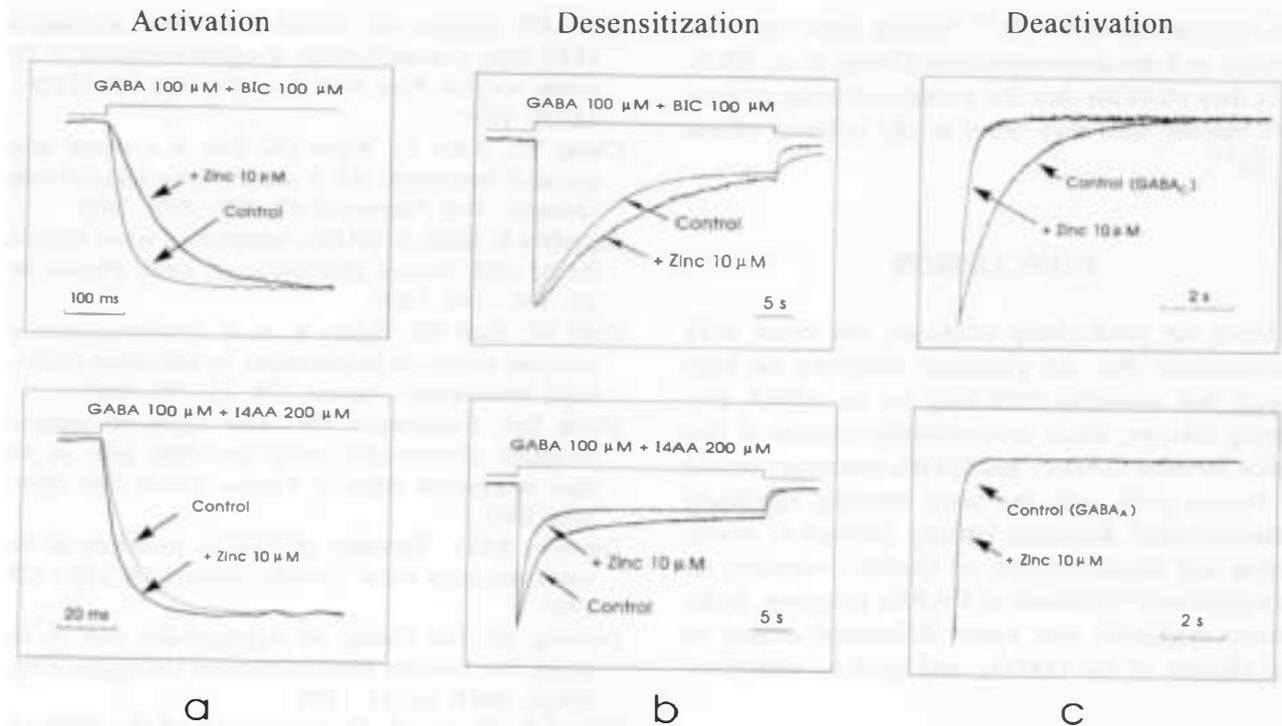


Fig. 7. Differential modulation by zinc of activation (a), desensitization (b) and deactivation (c) of GABA_C and GABA_A responses on bipolar cells. BIC, bicuculline. The effects of 10 μ M zinc on the GABA_C and GABA_A responses recorded from a single bipolar cell are shown in upper and lower panels, respectively. For comparison, control and Zn²⁺ responses were normalized. Note the differences in time scales for different panels. Adapted from Han & Yang (1999).

the Ca²⁺ 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 Zn²⁺, 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 Zn²⁺ is abundantly localized near the terminals of photoreceptors, suggesting that Zn²⁺ 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 Zn²⁺ 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 Zn²⁺ (Qian & Dowling, 1995; Qian et al, 1997). In regard to the modulation of GABA_A-induced responses by Zn²⁺ the results now available are inconsistent. Unlike significant potentiation of GABA_A responses by low concentration (0.1 ~ 100 μ M) of Zn²⁺ in skate bipolar cells (Qian et al, 1997), we consistently observed suppression of the GABA_A responses by Zn²⁺ on carp bipolar cells (Han & Yang, 1999).

Our recent results further showed that Zn²⁺ 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 Zn²⁺ 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

$\rho 1$ 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.

ACKNOWLEDGMENTS

We thank Dr. M. Sekiguchi of National Institute of Neuroscience (Tokyo, Japan) and Eli Lilly Corp. (US) for sending us PEPA and GYKI 53655 as gifts, respectively. This work was supported by grants from the Ministry of Science and Technology of China (Climbing Project), the National Foundation of Natural Science of China (No. 39670253, 39770256) and the National Research Center of Life Science of China (Shanghai).

REFERENCES

- Barnstable CJ. Glutamate and GABA in retinal circuitry. *Curr Opin Neurobiol* 3: 520–525, 1993
- Berger T, Schwartz C, Kraushaar U, Monyer H. Dentate gyrus basket cell GABA_A receptors are blocked by Zn^{2+} via changes of their desensitization kinetics: an *in situ* patch-clamp and single-cell PCR study. *J Neurosci* 18: 2437–2448, 1998
- Brandstätter JH, Hartvert E, Sassoepognetto M, Wässle H. Expression of NMDA and high-affinity kainate receptor subunit mRNAs in the adult rat retina. *Eur J Neurosci* 6: 1100–1112, 1994
- Brandstätter JH, Koulen P, Wässle H. Diversity of glutamate receptors in the mammalian retina. *Vision Res* 38: 1385–1397, 1998
- Calvo DJ, Vazquez AE, Milei R. Cationic modulation of R1-type γ -aminobutyrate receptors expressed in *Xenopus* oocytes. *Proc Natl Acad Sci USA* 91: 12725–12729, 1994
- Chang YC, Amin JS, Weiss DS. Zinc is a mixed antagonist of homomeric $\rho 1$ γ -aminobutyric acid-activated channels. *Mol Pharmacol* 47: 595–602, 1995
- Cherubini E, Strata F. GABA_C receptors: a novel receptor family with unusual pharmacology. *News Physiol Sci* 12: 136–141, 1997
- Cobb SR, Buhl EH, Halasy K, et al. Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature* 378: 75–78, 1995
- Dixon DB, Copenhagen DR. Two types of glutamate receptors differentially excite amacrine cells in the tiger salamander retina. *J Physiol (Lond)* 449: 589–606, 1992
- Djamgoz MBA. Diversity of GABA receptors in the vertebrate outer retina. *Trends Neurosci* 18: 118–120, 1995
- Dowling JE. The Retina: an Approachable Part of the Brain, The Belknap Press of Harvard University, Cambridge, 1987, pp. 81–123
- Eliasof S, Werblin F. Characterization of the glutamate transporter in retinal cones of the tiger salamander. *J Neurosci* 13: 402–411, 1993
- Feigenspan A, Wässle H, Bormann J. Pharmacology of GABA receptor Cl⁻ channels in rat retinal bipolar cells. *Nature* 361: 159–162, 1993
- Hamassaki-Britto DE, Hermans-Borgmeyer I, Heinemann S, et al. Expression of glutamate receptor genes in the mammalian retina: the localization of GluR1 through GluR7 mRNAs. *J Neurosci* 13: 1888–1898, 1993
- Han MH, Li Y, Yang XL. Desensitizing GABA_C receptors on carp retinal bipolar cells. *Neuro Report* 8: 1331–1335, 1997
- Han MH, Yang XL. Zn^{2+} differentially modulates kinetics of GABA_C vs GABA_A receptors in carp retinal bipolar cells. *Neuro Report* 10: 2593–2597, 1999
- Han MH, Yang XL. Differences in kinetics between GABA_C and GABA_A receptors on carp retinal bipolar cells. *Science in China* (submitted)
- Harrison NL, Gibbons SJ. Zn^{2+} : an endogenous modulator of ligand- and voltage-gated ion channels. *Neuropharmacol* 33: 935–952, 1994
- Hollmann M, Heinemann S. Cloned glutamate receptors. *Annu Rev Neurosci* 17: 31–108, 1994
- Hughes TE, Hermans-Borgmeyer I, Heinemann S. Differential expression of glutamate receptors genes (GluR1–5) in the rat retina. *Visual Neurosci* 8: 49–55, 1992
- Johansen TH, Chaudhary A, Verdoorn TA. Interactions among GYKI 52446, cyclothiazide, and aniracetam at recombinant AMPA and kainate receptors. *Mol Pharmacol* 48: 946–955, 1995

- Jones MV, Westbrook GL. The impact of receptor desensitization on fast synaptic transmission. *Trends Neurosci* 19: 96–101, 1996
- Konig P, Engel AK, Singer W. Integrator or coincidence detector? The role of the cortical neuron revisited. *Trend Neurosci* 19: 130–137, 1996
- Koulen P, Malitschek B, Kuhn R, Wässle H, Brandstätter JH. Group II and Group III metabotropic glutamate receptors in the rat retina: Distributions and developmental expression patterns. *Eur J Neurosci* 8: 2177–2187, 1996
- Jerma J, Morales M, Vicente MA, et al. Glutamate receptors of the kainate type and synaptic transmission. *Trends Neurosci* 20: 9–15
- Lu T, Shen Y, Yang XL. Desensitization of AMPA receptors on horizontal cells isolated from crucian carp retina. *Neurosci Res* 31: 123–135, 1998
- Lu T, Yang XL. Dissociation, pharmacology and physiological characteristics of retinal horizontal cells. *Chinese Journal of Neuroanatomy* 11: 299–306, 1995
- Lukasiewicz PD. GABA_A receptors in the vertebrate retina. *Mol Neurobiol* 12: 181–194, 1996
- McDonald RL, Olsen RW. GABA_A receptor channels. *Annu Rev Neurosci* 17: 569–602, 1994
- Matthews G, Ayoub GS, Heidelberger R. Presynaptic inhibition by GABA is mediated via two distinct GABA receptors with novel pharmacology. *J Neurosci* 14: 1079–1090, 1994
- Miller JF, Marc RE. GABAergic and glycinergic pathways in the inner plexiform layer of the goldfish retina. *J Comp Neurol* 291: 281–304, 1990
- Mosbacher J, Schoepfer R, Monyer H, et al. A molecular determinant for submillisecond desensitization in glutamate receptors. *Science* 266: 1059–1062, 1994
- Pan ZH, Lipton SA. Multiple GABA receptor subtypes mediate inhibition of calcium influx at rat retinal bipolar cell terminals. *J Neurosci* 15: 2668–2679, 1995
- Partin KM, Fleck MW, Mayer ML. AMPA receptor flip/flop mutants affecting deactivation, desensitization, and modulation by cyclothiazide, aniracetam, and thiocyanate. *J Neurosci* 16: 6634–6647, 1996
- Partin KM, Patneau DK, Mayer ML. Cyclothiazide differentially modulates desensitization of α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor splice variants. *Mol Pharmacol* 46: 129–138, 1994
- Partin KM, Patneau DK, Winters CA, et al. Selective modulation of desensitization at AMPA versus kainate receptors by cyclothiazide and Concanavalin A. *Neuron* 11: 1069–1082, 1993
- Qian H, Dowling JE. GABA_A and GABA_C receptors on hybrid bass retinal bipolar cells. *J Neurophysiol* 74: 1920–1928, 1995
- Qian H, Li L, Chappell RL, et al. GABA receptors of bipolar cells from the skate retina: actions of zinc on GABA-mediated membrane currents. *J Neurophysiol* 78: 2402–2412, 1997
- Sekiguchi M, Fleck MW, Mayer ML, et al. A novel allosteric potentiator of AMPA receptors: 4-[2-(Phenylsulfonylamino)ethylthio]-2,6-Difluorophenoxy acetamide. *J Neurosci* 17: 5760–5771, 1997
- Sekiguchi M, Takeo J, Harada T, et al. Pharmacological detection of AMPA receptor heterogeneity by use of two allosteric potentiators in rat hippocampal cultures. *Br J Pharmacol* 123: 1294–1303, 1998
- Shen Y, Lu T, Yang XL. Modulation of desensitization at glutamate receptors in isolated crucian carp horizontal cells by concanavalin A, cyclothiazide, aniracetam and PEPA. *Neurosci* 89: 979–990, 1999a
- Shen Y, Zhou Y, Yang XL. Characterization of AMPA receptors on isolated amacrine-like cells in carp. *Eur J Neurosci* 1999b, in press
- Sommer B, Keinänen K, Verdoorn TA, et al. Flip and flop: a cell-specific functional switch in glutamate-operated channels of the CNS. *Science* 249: 1580–1585, 1990
- Wilson M. Glutamate-gated channels in the outer retina. In: C. Peracchia (Ed.), *Handbook of Membrane Channels*, Academic Press, San Diego, 1994, pp. 287–302
- Wong LA, Mayer ML. Differential modulation by cyclothiazide and concanavalin A of desensitization at native α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid- and kainate-preferring glutamate receptors. *Mol Pharmacol* 44: 504–510, 1993
- Wu SM, Qiao X, Yang XL, et al. Localization and modulatory actions of zinc in vertebrate retina. *Vision Res* 33: 2611–2616, 1993
- Yang XL, Wu SM. Coexistence and functions of multiple types of glutamate receptor in the horizontal cells of the tiger salamander retina. *Vis Neurosci* 7: 377–382, 1991
- Yang XL, Wu SM. Feedforward lateral inhibition: Input-output relation of the horizontal cell to bipolar synapse in the tiger salamander retina. *Proc Natl Acad Sci USA* 88: 3310–3313, 1991
- Zhang DQ, Yang R, Yang XL. Suppression of sustained and transient on signals of amacrine cells by GABA is mediated by different receptor subtypes. *Science in China* 42: 395–400, 1999
- Zhang DQ, Yang XL. OFF pathway is preferentially suppressed by the activation of GABA_A receptors in carp retina. *Brain Res* 759: 160–162, 1997
- Zhou ZJ, Fain GL. Neurotransmitter receptors of starburst amacrine cells in rabbit retinal slices. *J Neurosci* 15: 5334–5345, 1995