REVIEW

GABAergic neurotransmission and retinal ganglion cell function

E. Popova

Abstract Ganglion cells are the output retinal neurons that convey visual information to the brain. There are ~20 different types of ganglion cells, each encoding a specific aspect of the visual scene as spatial and temporal contrast, orientation, direction of movement, presence of looming stimuli; etc. Ganglion cell functioning depends on the intrinsic properties of ganglion cell's membrane as well as on the excitatory and inhibitory inputs that these cells receive from other retinal neurons. GABA is one of the most abundant inhibitory neurotransmitters in the retina. How it modulates the activity of different types of ganglion cells and what is its significance in extracting the basic features from visual scene are questions with fundamental importance in visual neuroscience. The present review summarizes current data concerning the types of membrane receptors that mediate GABA action in proximal retina; the effects of GABA and its antagonists on the ganglion cell light-evoked postsynaptic potentials and spike discharges; the action of GABAergic agents on centre-surround organization of the receptive fields and feature related ganglion cell activity. Special emphasis is put on the GABA action regarding the ON–OFF and sustained–transient ganglion cell dichotomy in both nonmammalian and mammalian retina.

Keywords GABA · GABA receptors · Ganglion cells · Retina

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Introduction

Ganglion cells (GCs) are the output neurons of the retina that deliver a rich set of visual information to the brain. They are classified usually by their morphology or physiology. A common morphological feature of the most mammalian retinas is the α- and β-type ganglion cells and their homologs in primates parasol and midget cells (reviews: Wässle and Boycott 1991; Masland 2001; Troy and Shou 2002). Alpha (or parasol) retinal ganglion cells have large somata, large dendritic fields, large diameter axons with fast conduction velocity, and are most dense in the peripheral retina. Beta (or midget) retinal ganglion cells have smaller diameter somata, smaller dendritic fields, small diameter axons with slow conduction velocity, and predominate in the central retina. Midget ganglion cells have been called P cells, reflecting their projection to the parvocellular layers of the lateral geniculate nucleus, while parasol cells are termed M cells, reflecting their projection to the magnocellular layer of the lateral geniculate nucleus (Shapley and Perry 1986).

Retinal ganglion cells can be classified functionally into two categories according to their receptive field organization: (1) simple cells with concentric receptive fields and (2) complex cells with asymmetric receptive fields. The simple cells with concentric receptive fields are classified as ON and OFF depending on stimulus that produces an excitatory response (review: Dowling 2012). Ganglion cells of this type are often called contrast-sensitive units, because they respond best when there is maximum contrast between the center and surround stimuli. The ON and OFF ganglion cells appear as sustained and transient subtypes and as brisk and sluggish subtypes. The transient cells respond to standing contrast only at moment of exposure and their discharge returns to the unstimulated value

in a few seconds, while the discharge of the sustained cells remains above the maintained level as long as the target is present. Sluggish cells are characterized by low spontaneous activity, low maximum firing frequency, relatively slow responses to conventional visual stimuli and slowly conducting axons. Enroth-Cugell and Robson (1966) categorized ganglion cells in the cat retina as either X cells or Y cells, depending on their response characteristics under stimulation with reversing gratings. X cells respond to a drifting grating by modulating firing at the drift frequency (linear response). Y cells respond to a contrast reversing grating by modulating firing at twice the reversal frequency (nonlinear response). The X cells behave very much like the sustained ON or OFF GCs, whereas the Y cells respond transiently at the onset or cessation of illumination (Victor and Shapley 1979). Alpha (or parasol) cells are the morphological counterpart of brisk transient or Y cells, whereas beta (or midget) cells correspond to brisk sustained or X cells (Cleland et al. 1975; Peichl and Wässle 1981; Fukuda et al. 1985). In cat retina, eight different types of concentric ganglion cells have been described: brisk-sustained ON, brisk-sustained OFF, brisk-transient ON, brisk-transient OFF, sluggish-sustained ON, sluggish-sustained OFF, sluggish-transient ON, sluggish-transient OFF (Cleland and Levick 1974).

The complex ganglion cells with asymmetric receptive fields function to extract some basic features from visual scene as orientation, direction of movement, presence of looming stimuli, etc. In rabbit retina, six complex ganglion cell types have been described: ON–OFF direction selective, ON direction selective, orientation selective, local edge detector, large field, and uniformity cells (Levick 1967). There are four populations of direction selective ON–OFF GCs, which respond to both bright and dark objects moving over a broad range of speeds in one of the four directions and three populations of direction selective ON GCs, which respond to bright objects moving at slow speeds in one of the three directions (reviews: Demb 2007; Taylor and Smith 2011). There is also recent evidence for further functional subdivision of direction selective ON GCs into transient and sustained types, each of which has distinct anatomical features (Kanjhan and Sivyer 2010). Roska et al. (2006) made an attempt to gain an intuitive sense for how the visual world is represented in space–time by different classes of ganglion cells. They have demonstrated a great diversity of ganglion cell activity, measured using the space–time plots in rabbit retina. The authors have characterized 11 types of ganglion cells: (1) ON parasol cell; (2) ON bistratified cell; (3) ON delta cell, which is likely ON direction selective cell; (4) local edge detector; (5) ON–OFF direction selective cell; (6) ON beta cell; (7) OFF beta cell; (8) OFF parasol cell; (9) OFF coupled cell; (10) OFF delta cell and (11) ON alpha cell. Each of these types receives unique combination of excitatory and inhibitory inputs that modulate the cell's spiking activity in space and time.

The function of all ganglion cell types depends on the intrinsic properties of their membrane as well as on the excitatory and inhibitory inputs that they receive from bipolar and amacrine cells. It is known that retinal ganglion cells receive two functionally distinct types of light-driven inhibitory synaptic input: transient and sustained. Transient inhibition is activated at the onset and termination of a steady light stimulus (Werblin 1977; Wunk and Werblin 1979; Cohen 1998; Chen et al. 2010) or by certain types of appropriately moving stimuli (Werblin 1972; Werblin and Copenhagen 1974; Marchiafava 1979). Transient inhibition is present in ON, OFF and ON–OFF GCs, although its strength may vary in different cells. In addition, ganglion cells also receive sustained inhibitory input, which hyperpolarizes the ON ganglion cells in darkness and hyperpolarizes the OFF ganglion cells during steady illumination of the receptive field centre (Belgum et al. 1982, 1987; Cohen 1998; Chen et al. 2010). Light-evoked sustained inhibition has also been demonstrated in some ON–OFF ganglion cells (Belgum et al. 1983). Knowing the nature of neurotransmitters that mediate these distinct types of inhibition is an important prerequisite for understanding retinal physiology. GABA is one of the most abundant inhibitory neurotransmitters in the vertebrate retina. Its significance for ganglion cell functioning has been investigated in great number of studies, but the results obtained are in many aspects controversial. It is not resolved yet if the GABAergic system influences all types of retinal ganglion cells or its action possesses ON–OFF and sustained-transient asymmetry. Still open remains the question how the different types of GABA receptors participate in its action on retinal ganglion cells. The present review summarizes current data concerning the GABA actions on retinal ganglion cells in both nonmammalian and mammalian species.

GABAergic neurons in retina

Gamma-aminobutyric acid (GABA) fulfills all the criteria needed to establish a substance as a neurotransmitter in the retina. GABA is present in high concentration in some retinal neurons, which have high activity of L-glutamate decarboxylase (GAD—the major synthesizing enzyme for GABA) and high-affinity uptake system for GABA to terminate its transmitter action. They release GABA during depolarization or in response to a number of stimuli including light. GABA receptors have been well demonstrated in the retina (reviews: Yazulla 1986; Wu and Maple 1998; Yang 2004; Eggers et al. 2006).

Fig. 1 A schematic representation of GABA receptors. Ionotropic GABA$_A$ and GABA$_C$ receptors consist of five subunits that form a transmembrane chloride ion channel. The subunit composition of GABA$_A$ (*left*) and GABA$_C$ receptor (*right*) is indicated. The locations of the binding sites for GABA, GABA modulators (barbiturates, benzodiazepins) and antagonists (picrotoxin) are also shown. Metabotropic GABA$_B$ receptors consist of two subunits (B$_1$ and B$_2$) each of them having seven transmembrane domains. B$_1$ subunit bins GABA, while B$_2$ subunit is coupled to G protein that inhibits (via αi/o) adenylyl cyclase (AC) or regulates (via βγ) ion channels. With + is shown that βγ activates K$^+$ channels; with − is shown that βγ inhibits Ca^{2+} channels
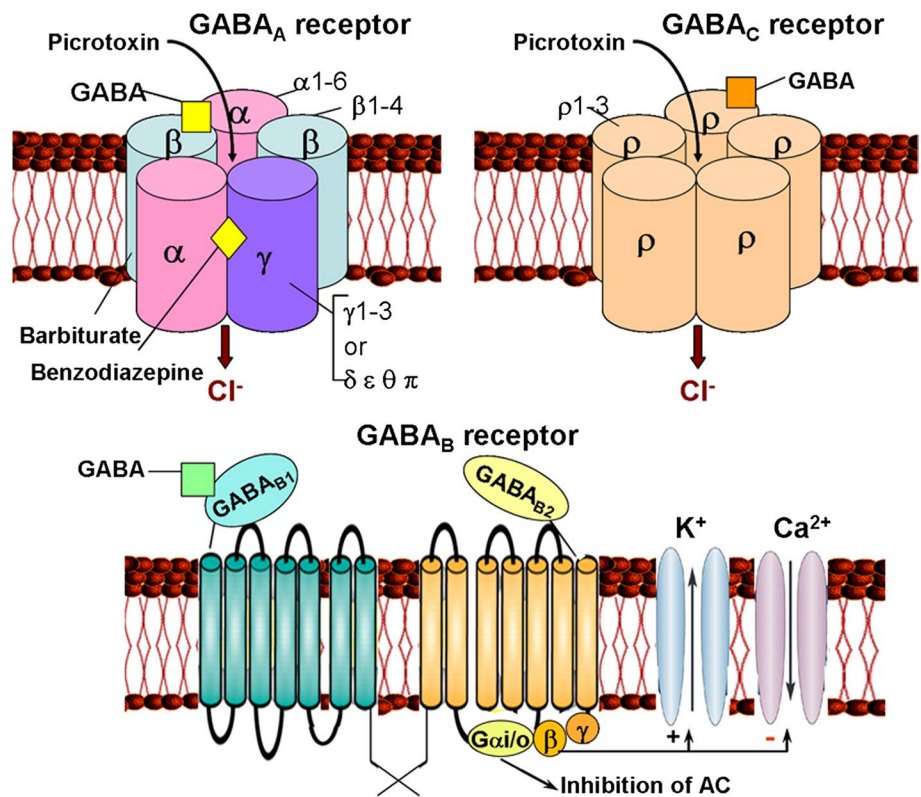
All vertebrate species have a large population of GABAergic neurons identified as amacrine cells and displaced amacrine cells (reviews: Yazulla 1986; Marc 1992). The GABAergic amacrine cells form a dense and heterogeneous population of cells branching at all levels of the inner plexiform layer. They are of ON, OFF or ON–OFF functional types. In mammalian retina, some of the GABAergic neurons in the inner nuclear layer are GABAergic interplexiform cells (review: Popova 2014). There is strong evidence that GABA is neurotransmitter also of some types of horizontal, bipolar and ganglion cells in nonmammalian and mammalian retina (reviews: Yazulla 1986; Marc 1992; Popova 2014).

GABA receptors in the retina

Physiological actions of GABA are mediated by two types of membrane receptors: ionotropic (GABA$_A$ and GABA$_C$) and metabotropic (GABA$_B$) receptors.

Ionotropic GABA receptors

GABA$_A$ receptors (GABA$_A$-R) are transmembrane proteins that consist of five subunits arranged around a central chloride ion-selective pore (reviews: Macdonald and Olsen 1994; Enz and Cutting 1998; Ogurusu et al. 1999; Olsen

and Sieghart 2008, 2009). There are 19 genes for GABA$_A$-R subunits, which include 16 subunits (α 1–6, β 1–3, γ 1–3, δ, ε, π, θ) that combined as GABA$_A$, and 3 rho (ρ) subunits, which contribute to what have been called GABA$_C$ receptors. The GABA$_C$ receptors are considered by the Nomenclature Committee of IUPHAR to be subtypes of GABA$_A$-R containing the ρ subunits. However, the ρ subunits are not simply equivalent to GABA$_C$ receptors, because some regions of the nervous system seem to lack ρ subunits and yet exhibit GABA$_C$-R pharmacology (review: Olsen and Sieghart 2008). In addition, certain GABA ρ subunits can co-assemble with the γ_2 subunit of GABA$_A$ receptor to form a heteromeric receptor with electrophysiological properties that correspond more closely to the native GABA$_C$ receptor on retinal neurons (Pan and Qian 2005). The term GABA$_C$ receptor is chosen to be used in the present review instead of GABAρ receptor, because most of the works cited are functional, where the GABA receptor subunit composition has not been identified. This term has been used in the original papers of all the authors working on vertebrate retina, whose results are commented in the present review.

It is known that each GABA$_A$ receptor has two binding sites for GABA, which are located at the interfaces between the alpha and beta subunits (Fig. 1). To these, binding sites bind selective agonists as muscimol, isoguvacine, THIP, ZAPA. Competitive GABA$_A$ receptor antagonists are

Table 1 GABA receptor expression in retinal neurons that make synaptic contacts in the inner plexiform layer, autoradiography, immunocytochemistry and in situ hybridization

Retinal cell type	GABA$_A$R	References	Speices	GABA$_C$R	Reference
Bipolar cell axon terminals			Frog	+	Vitanova et al. (2001)
			Turtle	+	Vitanova et al. (2001)
			Fish	+	Koulen et al. (1997)
			Chick	+	Koulen et al. (1997)
	+	Greferath et al. (1994), Fletcher et al. (1998)	Rabbit	+	Fletcher et al. (1998)
			Cat	+	Enz et al. (1996), Koulen et al. (1997)
	+	Brecha et al. (1991), Fletcher et al. (1998)	Rat	+	Enz et al. (1996), Koulen et al. (1998a), Fletcher et al. (1998)
	+	Schubert et al. (2013)	Mouse	+	Schubert et al. (2013)
	+	Vardi and Sterling (1994)	Monkey	+	Enz et al. (1996)
	+	Vardi and Sterling (1994)	Human		
Amacrine cells			Frog	+	Vitanova et al. (2001)
	+	Yazulla et al. (1989)	Chick		
	+	Brandstätter et al. (1995), Greferath et al. (1993, 1995), Brecha et al. (1991)	Rat		
	+	Greferath et al. (1994), Zucker and Ehinger (1998)	Rabbit		
	+	Hughes et al. (1991), Grünert and Hughes (1993)	Cat		
Ganglion cells	+	Koulen et al. (1996), Greferath et al. (1993), Brecha et al. (1991), Yen et al. (1996)	Rat		
	+	Koulen et al. (1996), Greferath et al. (1994), Rotolo and Dacheux (2003a, b)	Rabbit	+	Rotolo and Dacheux (2003b)
	+	Hughes et al. (1991), Grünert and Hughes (1993)	Cat		
	+	Hughes et al. (1989), Grünert et al. (1993), Macri et al. (2000)	Monkey		

bicuculline and SR95531, while picrotoxin and TBPS are blockers of chloride channel (Bormann 1988; Feigenspan and Bormann 1994). The GABA$_A$ receptors have modulatory binding sites for benzodiazepines, barbiturates, ethanol and neurosteroids (review: MacDonald and Olsen 1994; Olsen and Sieghart 2008, 2009). GABA$_A$ receptor subunits have been localized on almost all retinal neurons (review: Popova 2014) including amacrine and ganglion cells (Table 1). Bipolar cell terminals that synapse with third-order retinal neurons in the inner plexiform layer also possess GABA$_A$ receptors (Table 1). Some data indicate that GABA$_A$ receptors are localize in both sublaminae (a and b) of the inner plexiform layer (Greferath et al. 1994; Vardi and Sterling 1994; Enz et al. 1996; Wässle et al. 1998; Grünert 2000; Macri et al. 2000), suggesting that the ON as well as the OFF ganglion cells may receive GABA$_A$-R mediated input.

The GABA$_C$ receptors are composed entirely of rho (ρ) subunits. The three ρ subunits (ρ_1, ρ_2 and ρ_3) form homopentameric or heteropentameric complexes (Fig. 1), but

the exact molecular composition of native receptors is yet to be determined. GABA$_C$ receptors are selectively activated by (+)-cis-2-aminomethylcyclopropane-carboxylic acid [(+)-CAMP] and blocked by (1,2,5,6-Tetrahydropyridin-4-yl)methylphosphinic acid (TPMPA). They are also blocked by picrotoxin, but not bicuculline and SR95531. In some species (rat), however, picrotoxin does not block retinal responses mediated by GABA$_C$ receptors (Feigenspan et al. 1993; Pan and Lipton 1995) or it has variable effects on them (Yeh et al. 1996). It has been shown that heterodimeric nature ($\rho_1\rho_2$) of rat GABA$_C$ receptors underlies their lower (or absent) sensitivity to picrotoxin (Zhang et al. 1995). GABA$_C$ receptors are not modulated by many GABA$_A$ receptor modulators such as barbiturates, benzodiazepines, and neuroactive steroids. It is known that GABA$_C$ receptors are about 10-fold more sensitive to GABA than GABA$_A$ receptors and, thus, are activated by lower concentrations of GABA (Feigenspan and Bormann 1994; Chang and Weiss 1999). They respond more slowly

to GABA and mediate more prolonged inhibitory signals (Chang and Weiss 1999). The distribution of $GABA_C$ receptors in the retina is more limited than $GABA_A$ receptors. They are most abundant on bipolar cell axon terminals, but occasionally they have also been localized on cones, some horizontal cells, amacrine and ganglion cells (review: Popova 2014) (Table 1). The $GABA_C$ receptors on bipolar cell axon terminals mediate large tonic inhibitory currents (reviews: Lukasiewicz et al. 2004; Hull et al. 2006; Palmer 2006; Herrmann et al. 2011). The prolonged time course of this $GABA_C$ feedback inhibition is particularly suited to regulating sustained exocytosis from bipolar cells (Vigh and von Gersdorff 2005) and thus to shape the temporal properties of the glutamate signal from bipolar cells to ganglion cells. $GABA_C$ receptors are often found with $GABA_A$ receptors on bipolar cell terminals, but they are not co-localized at the same synaptic sites (Fletcher et al. 1998; Koulen et al. 1998a; Vitanova et al. 2001), suggesting that they may be activated by distinct GABAergic cell types (Palmer 2006).

Metabotropic GABA receptors

$GABA_B$ receptors are metabotropic receptors, which function as an obligatory heterodimers of the subunits $GABA_{B1}$ and $GABA_{B2}$ (Fig. 1). Until recently, the only firmly established molecular diversity consisted of two $GABA_{B1}$ subunit isoforms, $GABA_{B1a}$ and $GABA_{B1b}$, which assemble with $GABA_{B2}$ subunits to generate heterodimeric $GABA_{B1a,2}$ and $GABA_{B1b,2}$ receptors. Only $GABA_{B1}$ can bind ligands (such as GABA and baclofen) and orthosteric antagonists. $GABA_{B2}$ increase agonist affinity of $GABA_{B1}$ and is also responsible for G-protein coupling. $GABA_B$ receptors associate specifically with Gi/o G-proteins that regulate voltage-gated Ca^{2+} channels, G-protein activated inwardly rectifying K^+ channels, and adenylyl cyclase (reviews: Ong and Kerr 2000; Bettler et al. 2004; Padgett and Slesinger 2010; Pinard et al. 2010). It is generally believed that the modulation of Ca^{2+} channels regulates presynaptic transmitter release, while modulation of K^+ channels and adenylyl cyclase activity is important in hyperpolarizing postsynaptic neurons. However, it has been shown that baclofen suppresses current through high-voltage-activated (N type) calcium channels (tiger salamander, Zhang et al. 1997a; Shen and Slaughter 1997), but enhances current through L-type calcium channels in ganglion cell membrane (tiger salamander, Shen and Slaughter 1999). Suppressed calcium currents possibly through L-type calcium channels by baclofen have been seen in ganglion cells dissociated from adult goldfish retina (Bindokas and Ishida 1991). Agonists of $GABA_B$ receptors are baclofen, 3-aminopropyl phosphonic acid, lesogaberan (AZD-3355), CGP-44532. Selective

antagonists of $GABA_B$ receptors are phaclofen, saclofen, 2-hydroxysaclofen, SCH-50911, CGP-35348, CGP-52432, CGP 54626, CGP-55845.

$GABA_B$ receptors have been found presynaptically and/or postsynaptically on horizontal cells (rat, Koulen et al. 1998b; mouse, Zhang et al. 1998; frog, Zhang and Yang 1999), amacrine cells (rat, Koulen et al. 1998b; Nehring et al. 2000; mouse, Zhang et al. 1998), ganglion cells (rat, Koulen et al. 1998b; mouse, Zhang et al. 1998; rabbit, Rotolo and Dacheux 2003a, b) and Muller glial cells (frog, Zhang and Yang 1999). It has been shown that $GABA_BR_{1a}$ transcripts are detected in horizontal, amacrine and ganglion cells, while $GABA_BR_{1b}$ is detected only in ganglion cells in mouse retina (Zhang et al. 1998). Two functional types of $GABA_B$ receptors have been demonstrated in amphibian ganglion cells: one sensitive to baclofen and another sensitive to *cis*-aminocrotonic acid (CACA) (Zhang et al. 1997a). They downregulate different types of calcium channels. While a large fraction of baclofen effect is on the N-type calcium channel, the action of CACA is predominantly at the dihydropyridine-sensitive calcium channel. $GABA_B$ immunoreactivity has not been reported in bipolar cells, although $GABA_B$ receptor-mediated inhibition of calcium currents has been demonstrated in bipolar axon terminals in nonmammalian retina (goldfish, Heidelberger and Matthews 1991; Matthews et al. 1994; tiger salamander, Maguire et al. 1989). Maguire et al. (1989) suggest that $GABA_B$ receptors modulate not only the calcium current but also transmitter release by a pathway involving G proteins.

GABA effects on ganglion cells

The effects of GABA and GABA-related agents (agonists and antagonists) on ganglion cell activity are investigated in two main manners: (1) by analyzing the changes in membrane potential and light-evoked synaptic potentials—excitatory postsynaptic potentials (EPSP) or currents (EPSCs) and inhibitory postsynaptic potentials (IPSPs) or currents (IPSCs) and (2) by analyzing the changes in spontaneous and light-evoked spike activity. The first method can reveal the mode of GABA action—presynaptic or postsynaptic and thus could give insight into the synaptic interactions in the inner plexiform layer. However, the changes of synaptic input not always cause changes of the spiking output of retinal ganglion cells. This disadvantage is overcome by the second method, which gives reliable information about the significance that the GABAeric system has for the retinal output to the brain. The results obtained by these two manners of investigation are presented consequently in the review.

Effects on membrane potential and light-evoked postsynaptic potentials

Effects of GABA and GABA antagonists in nonmammalian retina

Postsynaptic action   It has been shown that exogenously applied GABA causes a hyperpolarization of the membrane potential and an increase in membrane conductance of almost all ganglion cells in nonmammalian species (mudpuppy, Miller et al. 1981; Belgum et al. 1984; Slaughter and Bai 1989; tiger salamander, Zhang and Slaughter 1995; turtle, Vigh and Witkovsky 2004). The effect persists in the presence of Co^{2+} (which block the synaptic transmission), indicating that GABA activates GABA receptors intrinsic to the ganglion cells. The postsynaptic mode of GABA action on GCs is supported also by the results obtained with application of GABA receptor antagonists. The ionotropic GABA receptor antagonists (picrotoxin and bicuculline) cause an increase of the input resistance in all ganglion cells, suggesting that all these cells are tonically affected by continuous release of GABA, which opens chloride channels (mudpuppy, Miller et al. 1981). The same antagonists eliminate almost all the spontaneous IPSPs (sIPSPs), recorded from ON–OFF GCs in tiger salamander retina (Gao and Wu 1998) and completely block the light-evoked transient ON and OFF IPSPs in some amphibian GCs irrespective of their type (ON–OFF, transient ON or transient OFF) (mudpuppy, Frumkes et al. 1981; Zhang et al. 1997b; tiger salamander, Zhang et al. 1997b). The latter results indicate that the GABAergic system is solely responsible for the transient inhibition, which occurs at both the onset and the offset of light stimulus in some, but not all amphibian GCs. Glycine mediates the transient inhibition in the rest of the cells (Frumkes et al. 1981). In a few amphibian ON–OFF ganglion cells, a mixed GABA-glycinergic inhibition at both stimulus onset and offset has been found and in still other cells hybrid GABAergic ON IPSPs and glycinergic OFF IPSPs have been registered (Frumkes et al. 1981). Some authors argue, however, that bicuculline (Daniels 1974) or picrotoxin (Belgum et al. 1984) is ineffective in blocking the light-evoked transient inhibition in any ganglion cells, even they block the sustained inhibitory input to them (Belgum et al. 1984). The cause for these contradictory results obtained in amphibian retina is unclear.

Some data indicate that GABA could modulate the IPSPs generated by other neurotransmitters. It has been demonstrated that antagonists of ionotropic GABA receptors caused an enhancement of the glycinergic IPSCs in all (tiger salamander, Cook et al. 2000; Song and Slaughter 2010) or ~1/3 of the amphibian ganglion cells (mudpuppy, Miller et al. 1981; Frumkes et al. 1981; tiger salamander, Zhang et al. 1997b). The effect can be seen immediately after blocker's application or it can develop slowly over the course of 5–20 min. It has been suggested that the rapid enhancement of the glycinergic inhibitory inputs is mediated primarily by $GABA_A$ receptors, because application of picrotoxin after SR95531 (selective $GABA_A$ receptor antagonist) does not further increase the peak amplitude of the inhibitory current (Zhang et al. 1997b). SR95531 causes the light-evoked IPSCs to become more transient, while picrotoxin makes them more sustained. The rapid enhancement of the IPSCs, caused by GABA antagonists, may be due "to a block of dark-released GABA influence on the ganglion cell, resulting in an increase of input resistance" (Miller et al. 1981; Frumkes et al. 1981), or to blocking of $GABA_A$ receptors on glycinergic amacrine cells leading to their disinhibition (Zhang et al. 1997b). Zhang et al. (1997b) suggest that "feedforward inhibition to ganglion cells is regulated by cross-inhibition between GABAergic and glycinergic amacrine cells" (Fig. 2). The slow enhancement of the glycinergic IPSCs, which occurs in the dark and mimics the effect of light adaptation, is caused only by picrotoxin, but not bicuculline (Cook et al. 2000). Cook et al. (2000) suggest that "the glycinergic inhibitory inputs are modulated by an unknown substance whose synthesis and/or release is inhibited in dark-adapted retinas by GABA acting at $GABA_C$ receptors".

Presynaptic action   The presynaptic action of GABA on the bipolar cell axon terminals modulates their release of glutamate and thus influences the EPSPs recorded from GCs. It has been demonstrated that GABA, acting through $GABA_C$ receptors, preferentially reduces the ON EPSPs of amphibian ON–OFF GCs, while the OFF EPSPs are nearly unaffected or reduced to a much lesser extent (Zhang and Slaughter 1995). A decreased amplitude of light-evoked EPSCs in amphibian ON–OFF GCs is seen also during blockade of GAT-1 transporter that resulted in accumulation of GABA in the retina (tiger salamander, Ichinose and Lukasiewicz 2002). GABA uptake blockade not only suppresses the EPSCs in GCs, but it shifts the V-log I function of the ON response to higher light intensities and broadens its dynamic range (Ichinose and Lukasiewicz 2002). Similar effects are seen during steady surround illumination or increased background illumination and they reflect decreased ganglion cell light sensitivity (Sakmann and Creutzfeldt 1969; Werblin 1974; Thibos and Werblin 1978). It has been demonstrated that the effects of GABA uptake blockade are due to increased activation of $GABA_C$, but not $GABA_A$ receptors on bipolar cell axon terminals (Ichinose and Lukasiewicz 2002). Thus, it appears that both exogenous GABA and GABA uptake blockade decrease glutamate release from bipolar cells mainly through $GABA_C$ receptors.

The *blockade of ionotropic GABA receptors* causes an enhancement of the EPSPs in some amphibian ON–OFF

Fig. 2 A summary diagram model for possible presynaptic and postsynaptic actions of GABA in nonmammalian retina. The model is suggested from the results of Zhang et al. (1997b), Tian and Slaughter (1994) and Song and Slaughter (2010). *BC* bipolar cell, *AC* amacrine cell, *GC* ganglion cell, *Gly* glycine, (−) inhibition, (+) enhancement; ? uncertain action
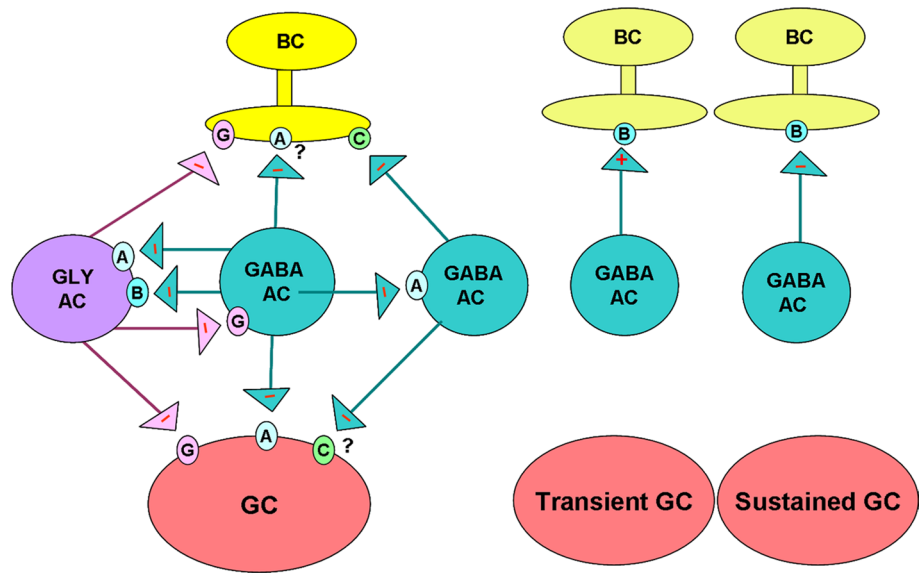
GCs, transient ON GCs and transient OFF GCs (mudpuppy, Miller et al. 1977; Frumkes et al. 1981; tiger salamander, Song and Slaughter 2010). The exact type of ionotropic GABA receptors ($GABA_A$, $GABA_C$ or both) that mediate this presynaptic action of the GABA antagonists is a matter of debate. Some authors argue that the blockade of $GABA_C$, but not $GABA_A$ receptors, is responsible for the enhancement of the peak amplitude and prolongation of transient ON and OFF EPSCs in ON–OFF GCs (tiger salamander, Shen and Slaughter 2001). This statement is in line with the results obtained with application of exogenous GABA and GABA uptake blockers. Other authors, however, insist that both $GABA_A$ and $GABA_C$ receptors modulate bipolar cell output, although in a different manner. Song and Slaughter (2010) presented data that the blockade of $GABA_A$ receptors increases the amplitude without altering the time course of the GC light-evoked EPSCs, while the blockade of $GABA_C$ receptors mainly prolongs their time course. Still other authors have found that the $GABA_A$ receptor blockade has opposite effects to that obtained during $GABA_C$ receptor blockade (tiger salamander Zhang et al. 1997b; Ichinose and Lukasiewicz 2005). Zhang et al. (1997b) have reported that the $GABA_A$ receptor blockade (with SR95531) causes a decrease in the duration of EPSPs, particularly the ON EPSPs, while subsequent application of picrotoxin prolongs the light-evoked ON and OFF EPSPs. Zhang et al. (1997b) suggest that a $GABA_C$ feedback pathway to bipolar cells produces a delay inhibition of transmitter release. That is why when the $GABA_C$ pathway is blocked, negative feedback is eliminated and bipolar cell output is prolonged. This $GABA_C$ pathway is itself inhibited by a $GABA_A$ pathway (Fig. 2). Thus, when the $GABA_A$ pathway is blocked, the $GABA_C$ pathway is disinhibited and the bipolar cells receive a stronger negative feedback, which results in more transient

input to the inner retina. Ichinose and Lukasiewicz (2005) have found that the $GABA_A$ receptor blockade (by bicuculline) reduces the amplitude and prolongs the duration of ON EPSCs in ON–OFF GCs. The authors suggest that the effect of bicuculline on the amplitude of the EPSCs is due to blockade of serial inhibitory pathway, while the prolongation of their duration is probably due to a direct $GABA_A$ receptor modulation of bipolar cell transmitter release.

The presynaptic action of endogenous GABA, mediated by *metabotropic GABA receptors,* shows clear transient-sustained asymmetry in some amphibian ganglion cells. It has been shown that $GABA_B$ receptor agonists (baclofen and 3-amino-propylphosphonic acid) augment both the ON and OFF EPSPs in amphibian transient ON–OFF GCs, while the blockade of $GABA_B$ receptors (by CGP35348 and CGP55845) causes a diminution of the transient ON and OFF EPSCs in a group of ganglion cells without altering their IPSCs (mudpuppy, tiger salamander, Slaughter and Bai 1989; Tian and Slaughter 1994; Song and Slaughter 2010). This indicates that the endogenous $GABA_B$ receptor activation directly enhances glutamate release from bipolar cells to one set of amphibian transient ganglion cells—effect opposite to that caused by activation of ionotropic GABA receptors (Tachibana and Kaneko 1988; Lukasiewicz and Werblin 1994; Pan and Lipton 1995; Lukasiewicz and Shields 1998; Shen and Slaughter 2001). In a second group of ganglion cells, an indirect pathway plays a role in enhancement of bipolar cell output (Song and Slaughter 2010). This pathway affects primarily the ON pathway and it includes $GABA_B$ receptors that inhibit glycinergic amacrine cell, which in turn disinhibits bipolar cell transmitter output (Fig. 2). This $GABA_B$ receptor-mediated serial pathway is normally occluded by retinal circuit that activates $GABA_A$ receptors and it is only

evident when $GABA_A$ receptors are inhibited. In a third and largest group of ganglion cells, blockade of $GABA_B$ receptors has no apparent effect on their EPSCs and IPSCs (Song and Slaughter 2010). In sustained GCs, the effects of baclofen and $GABA_B$ receptor antagonists are opposite to that described for the transient GCs (Slaughter and Bai 1989; Tian and Slaughter 1994). $GABA_B$ receptor blockade causes an enhancement of the amplitude and prolongation of the duration of their light-evoked EPSPs, suggesting that endogenous $GABA_B$ receptor activation acts to diminish the release of glutamate from presynaptic bipolar cells (Tian and Slaughter 1994). Thus, it appears that activation of $GABA_B$ receptors causes an enhancement of glutamate release from amphibian bipolar cells that synapse with transient GCs, but suppression of glutamate release from bipolar cells that synapse with sustained GCs (Fig. 2). It remains to be determined if different bipolar cells mediate these opposite actions or various synapses from a bipolar cell are differentially regulated.

Summary GABA has postsynaptic as well as presynaptic mode of action on nonmammalian retinal ganglion cells. The postsynaptic action appears to be mediated mainly by ionotropic GABA receptors, while the presynaptic action is mediated by both ionotropic and metabotropic GABA receptors. GABA is responsible for the transient IPSPs that occur at both stimulus onset and offset in some, but not all GCs. Its action can cause, however, a disinhibition of glycinergic amacrine cells and thus an enhancement of the IPSPs recorded from GCs. GABA influences the transmitter release from bipolar cell terminals and thus changes the EPSPs in postsynaptic GCs. The effects of its presynaptic action depend on the type of GABA receptors involved. While activation of ionotropic receptors in most cases diminishes the EPSPs of GCs, the activation of metabotropic receptors has diverse effects on them (no change, enhancement or diminution). It is not resolved yet if the activation of each type of ionotropic GABA receptors ($GABA_A$ and $GABA_C$) influences the amplitude and time characteristics of EPSPs and if their action possesses ON–OFF asymmetry in nonmammalian ganglion cells.

Effects of GABA and GABA antagonists in mammalian retina

Postsynaptic action Similarly to its action in nonmammals, GABA causes a hyperpolarization of the membrane potential and an increase in membrane conductance of mammalian ganglion cells (rodents, Tauck et al. 1988). Exogenously applied GABA elicits inhibitory currents in rabbit GCs in the presence of Co^{2+}, indicating that GABA activates GABA receptors intrinsic to the ganglion cells (Rotolo and Dacheux 2003a, b). It has been demonstrated that these currents are mediated by $GABA_A$ and $GABA_B$

receptors in transient OFF GCs, while in transient ON GCs they are mediated by $GABA_A$, $GABA_C$ and $GABA_B$ receptors in some cells and by $GABA_A$ and $GABA_C$ receptors in the others. All cells have large glycine-activated currents. Thus, it appears that all transient ON GCs express functional $GABA_A$, $GABA_C$, and glycine receptors, while all transient OFF GCs express functional $GABA_A$, $GABA_B$, and glycine, but no $GABA_C$ receptors.

Endogenously released GABA can generate spontaneous IPSPs in many mammalian ganglion cells and these sIPSPs appear to predominate over the glycinergic ones. It has been shown that $GABA_A$ antagonists (bicuculline and SR95531) completely block sIPSCs in 25 out of 37 GCs; strychnine completely blocks sIPSCs in 6 GCs. While in the other cells, combined application of bicuculline and strychnine is needed to abolish sIPSPs in light-adapted rat retina (Protti et al. 1997). All the cells respond to the application of both GABA and glycine independently of the nature of their synaptic input, indicating that all GCs are endowed with both $GABA_A$ and glycine receptors. Different results have been reported by Tian et al. (1998) in mouse retina, where bicuculline alone completely blocks the sIPSCs in one-half of the ganglion cells, while in the other one-half combined application of bicuculline and strychnine is needed to fully eliminate the sIPSCs. Strychnine alone could not completely eliminate the sIPSCs in any of the cells, indicating that none of the cells receives only glycine receptor-mediated input. The reasons behind the mouse/rat differences are unclear. Further studies in rodent and other mammalian retina should provide insight into whether these differences reflect variations in the selectivity by which presynaptic neurons contact the ganglion cells or simply variations in the spontaneous release of specific types of presynaptic neurons.

GABA can produce light-evoked IPSCs at both stimulus onset and offset in all ON GCs (transient and sustained ones) and transient OFF GCs, while the sustained OFF GCs receive only weak OFF, but not ON GABAergic feedforward inhibition (rabbit, Chen et al. 2010). The sustained ON GCs receive both ON and OFF glycinergic inhibition, while the other cell types receive only ON glycinergic inhibition. The GABAergic inhibition appears in two forms, which are probably mediated by different types of GABAergic amacrine cells: (1) local-sustained inhibition with long latency and (2) broad transient inhibition with short latency. Chen et al. (2010) suppose that broad, short latency GABAergic inhibition may be associated with saccadic suppression and objective motion sensitive response, while narrow field, long latency GABAergic inhibition is a good candidate for edge enhancement.

Presynaptic action It is reasonable to expect that blocking of the GABAergic feedback to bipolar cell terminals

could increase the release of glutamate and thus augment the EPSPs recorded in mammalian ganglion cells. It has been shown that the blockade of ionotropic GABA receptors causes an enhancement of EPSCs to large light spots in rabbit ON GCs, OFF GCs and ON–OFF GCs (Flores-Herr et al. 2001; Buldyrev and Taylor 2013). Flores-Herr et al. (2001) have also observed that the transient light-evoked currents become very sustained under the influence of picrotoxin and concluded that the GABAergic inhibition apparently influences both the amplitude and time course of the EPSCs. The GABAergic presynaptic suppression of bipolar cell output is mediated only by GABA$_C$ receptors in ON bipolar cells and both GABA$_A$ and GABA$_C$ receptors in OFF bipolar cells (Buldyrev and Taylor 2013). Thus, it appears that different types of ionotropic GABA receptors mediate presynaptic vs. postsynaptic action of GABA in rabbit ON and OFF channels. While only GABA$_C$ receptors mediate GABA presynaptic action on the ON bipolar cells, both GABA$_A$ and GABA$_C$ receptors mediate its postsynaptic action on the ON GCs. On the other hand, both GABA$_A$ and GABA$_C$ receptors mediate GABA presynaptic action on the OFF bipolar cells, while only GABA$_A$ receptors mediate its postsynaptic action on the OFF GCs (Fig. 3).

Summary GABA has postsynaptic and presynaptic mode of action in mammalian GCs similarly to its action in nonmammalian retina. However, a clear ON–OFF asymmetry of the ionotropic GABA receptors involved in both presynaptic and postsynaptic actions of GABA has been demonstrated in mammalian (rabbit) retina. The role of metabotropic GABA receptors in modulating the light-evoked IPSPs and EPSPs in mammalian GCs is largely unknown. It has not been demonstrated yet if GABA can disinhibit glycinergic amacrine cells and thus enhance the IPSPs recorded in ganglion cells as it has been shown in nonmammalian retina.

Effects on spike activity

Effects of GABA and GABA antagonists in nonmammalian retina

GABA consistently depresses the spontaneous and light-evoked spike activity of all ganglion cells irrespective of their physiological type (frog, Bonaventure et al. 1980; Backstrom 1981; Bonaventure and Wioland 1981; fish, Negishi et al. 1978; Glickman et al. 1982; Lasater and Lam 1984; Schellart et al. 1984; Cohen 1985; turtle, Ariel and Adolph 1985; chick, Liu et al. 2007). However, the effect of exogenous GABA may depend on the site and means of its application. It has been shown that GABA decreases the responses of all GCs types (ON, OFF, ON–OFF) during electrophoretic application at the IPL, while it causes similar or opposite changes in the cells during
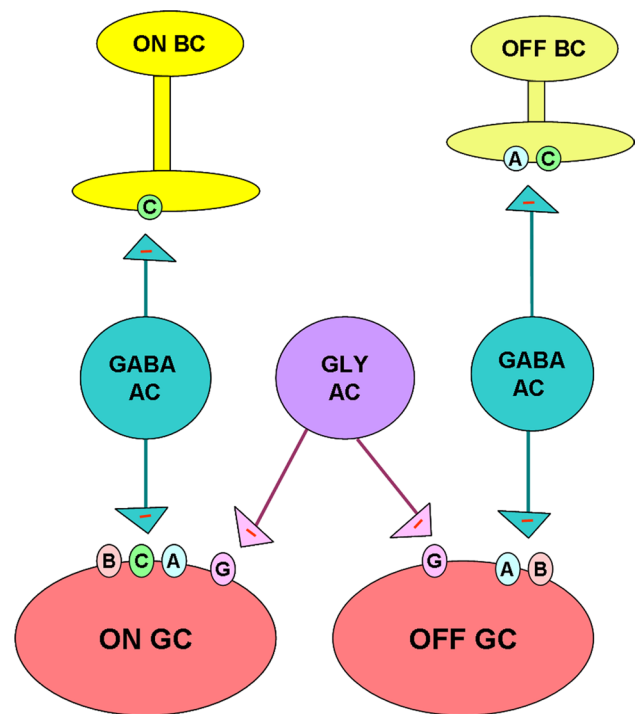

Fig. 3 A summary diagram model for possible presynaptic and postsynaptic actions of GABA in mammalian retina. The model is suggested from the results of Rotolo and Dacheux (2003a, b) and Buldyrev and Taylor (2013) for rabbit retina. The abbreviations are the same as in Fig. 2

its pressure-microinjection application at the OPL (fish, Negishi et al. 1978). When GABA is applied to the bathing medium, it suppresses the OFF responses and has no effect on the ON responses of GCs. It has been demonstrated that GABA increases, while picrotoxin and bicuculline attenuate, the medium correlations (with distributed time lag 19–30 ms) between transient ON–OFF GCs, indicating that the activation of GABAergic pathways allows the ganglion cells to fire more correlated spikes (Liu et al. 2007). Because TPMPA (selective GABA$_C$ receptor antagonist) has inconsistent effects on the firing rates and medium correlations, Liu et al. (2009) suggest that GABA$_A$, but not GABA$_C$ receptor-mediated inhibitory pathway, plays a crucial role in the regulation of correlated activities among neighborhood neuronal population. GABA$_A$ receptors are probably also a target of spontaneously released GABA, because their blockade with bicuculline increases the spontaneous discharges of transient GCs (mudpuppy, turtle, Daniels 1974) and sustained ON and OFF GCs (fish, Lasater and Lam 1984).

How the endogenous GABA influences the individual GCs in a given type is an open question. Some authors argue that GABA influences all cells in a similar manner, while other authors suggest that its action possesses some individual specificity. The first statement is supported by
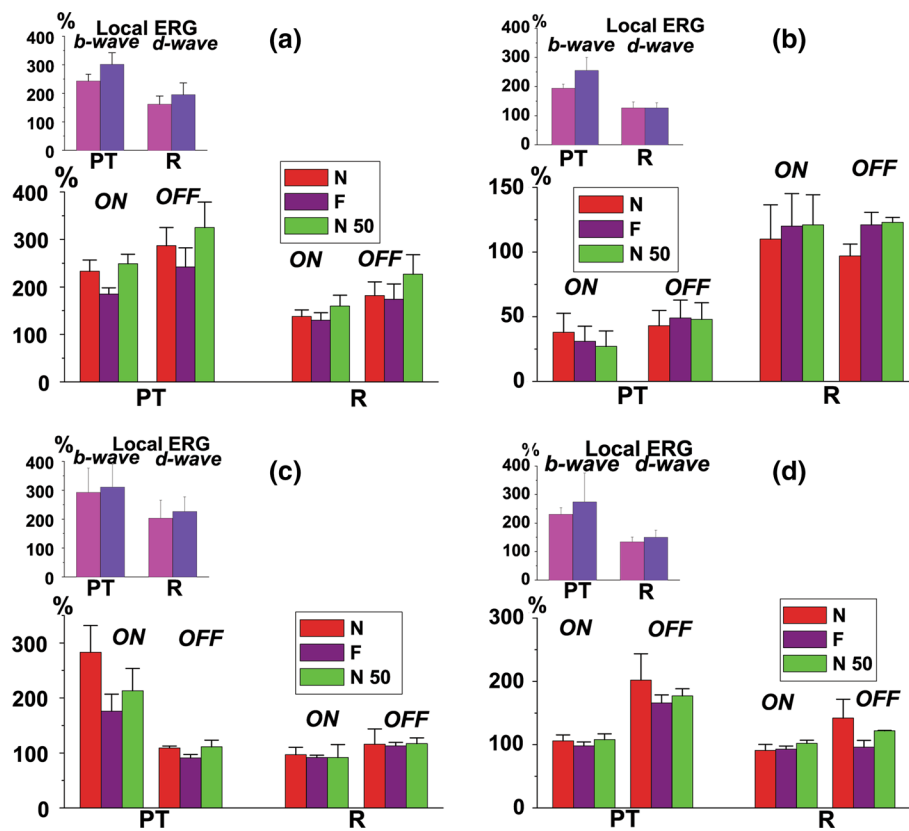
Fig. 4 Effects of picrotoxin on the light responses of frog ON–OFF ganglion cells and local ERG. Changes of mean number of impulses (N), peak frequency (F) and number of impulses in the first 50 ms (*N* 50) of the responses expressed as % from their initial values are shown during the perfusion with picrotoxin (PT) and with Ringer solution in the recovery period (*R*). The mean ± SEM are represented. At the *tops* changes of the amplitude of the b- and d-waves of the local ERG (mean ± SEM), expressed as % from its initial value. The ERG was recorded simultaneously with the GCs' activity during perfusion with picrotoxin (PT) and with Ringer solution in the recovery period (R). **a** Ganglion cells with enhanced ON and OFF responses during the perfusion with PT. **b** Ganglion cells with diminished ON and OFF responses during the perfusion with PT. **c** Ganglion cells with enhanced ON and unaltered OFF responses during the perfusion with PT. **d** Ganglion cells with unaltered ON and enhanced OFF responses during the perfusion with PT

data showing that the blockade of ionotropic GABA receptors (by picrotoxin) causes a considerable increase in number of impulses in both the ON and OFF responses in all ON–OFF GCs (frog, Bonaventure et al. 1980; Backstrom 1981; chick, Liu et al. 2007) and transient ON GCs (tiger salamander, Bieda and Copenhagen 2000). The enhancing effect of picrotoxin on ganglion cell spike activity is evident when stimuli with different size (small, medium and large) and different intensities are applied (Backstrom 1981). These results suggest that all ganglion cells tested are under inhibitory GABAergic influences mediated through ionotropic GABA receptors. It has been demonstrated that the effect of picrotoxin on the absolute sensitivity of the responses, however, depends on the type of the photoreceptor input. Picrotoxin increases the sensitivity of the cone-mediated responses, but decreases the sensitivity of the rod-mediated responses (Backstrom 1981). Isolated GABA$_A$ receptor blockade (by bicuculline) also increases the sensitivity of cone-mediated responses in all

ON and OFF GCs in fish retina (Lasater and Lam 1984), while in mudpuppy and turtle retinas it increases the OFF responses, but diminishes the ON responses in GCs (Daniels 1974). The individual specificity of GABA action upon GCs is supported by our data showing that picrotoxin does not change the light responses in 6 out of 63 GCs irrespective of their type, while it has diverse effects in the other cells (Popova et al. 2003). Picrotoxin causes an enhancement of both the ON and OFF responses in some ON–OFF GCs (24 out of 42) (Fig. 4a), while in the other cells (*n* = 8) it decreases their ON and OFF responses (Fig. 4b) or it increases the one response and does not change the other (Fig. 4c, d). These results are in good agreement with the results obtained in other amphibians (mudpuppy, tiger salamander), where IPSCs from ON–OFF GCs were recorded during picrotoxin treatment. It has been shown that picrotoxin has diverse effects on these currents—it may suppress (Miller et al. 1981; Frumkes et al. 1981) or enhance them (Frumkes et al. 1981; Zhang et al. 1997a,

Fig. 5 Effects of picrotoxin on the light responses of frog ON and OFF ganglion cells. The ganglion cell responses are presented as poststimulus time histograms (PSTHs). The PSTHs were obtained during the control period (R-upper histogram), during the perfusion with picrotoxin (PT) and during the period of recovery (R-lower histogram). **a** PSTHs from one ON GC that became ON–OFF under the influence of PT. **b** PSTHs from one OFF GC that became ON–OFF under the influence of PT. **c** PSTHs from one tonic OFF GC with greatly diminished tonic component under the influence of PT. **d** PSTHs from one tonic OFF GC with markedly potentiated OFF response under the influence of PT. The stimulus onset and offset are indicated below the histograms. Calibration: time—0.1 s; amplitude—1 impulse
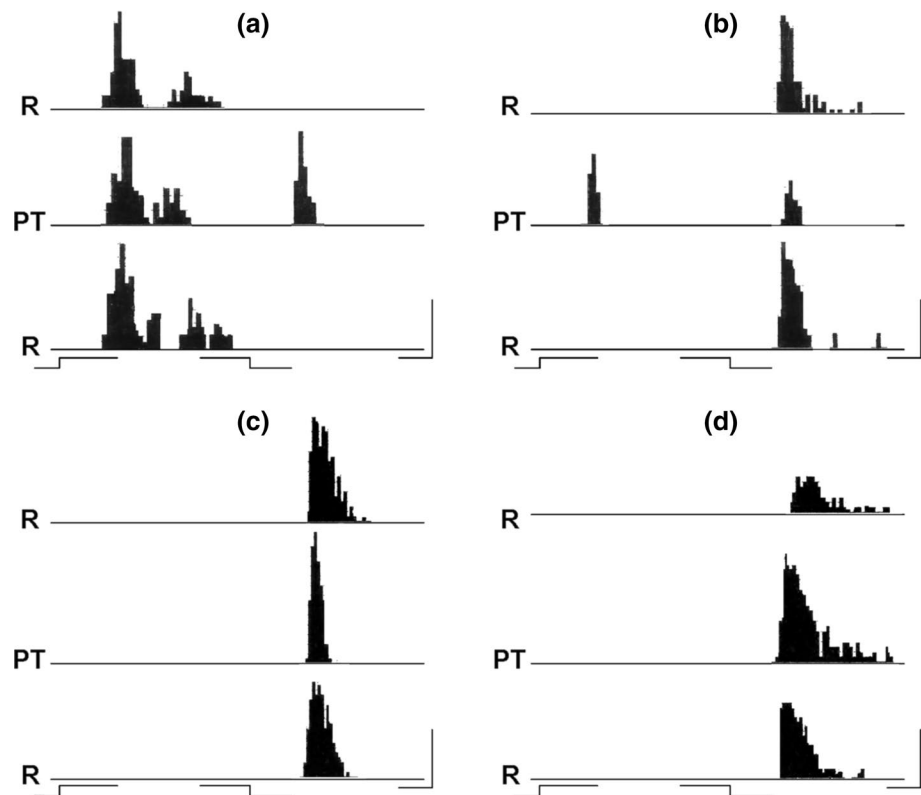
b; Cook et al. 2000). Moreover, the blocker may influence the synaptic currents to both onset and termination of the light stimulation or it may affect them separately. We have obtained (Popova et al. 2003) that picrotoxin has diverse effects also upon the OFF GCs irrespectively of their subtype (sustained or transient)—it may increase or decrease their light responses. The blocker may alter the apparent type of some ON and OFF GCs, which become ON–OFF GCs, because of appearance of a new response (Fig. 5a, b). Similarly, a prominent ON EPSPs in OFF GCs and prominent OFF EPSPs in ON GCs become evident when the IPSPs are blocked by picrotoxin in mudpuppy retina (Frumkes et al. 1981). These observations raise the possibility that some ON and OFF cells are actually a variation of ON–OFF neurons, whose response is masked by the GABAergic inhibition. We recorded local ERG simultaneously with ganglion cell activity to give an insight into the retinal site of picrotoxin action. It is known that the ERG b-wave (ON response) and d-wave (OFF response) depend mainly on the activity of the ON and OFF bipolar cells in distal retina (reviews: Perlman 1995; Frishman 2006). We have demonstrated that picrotoxin increases the amplitude of both the b-and d-waves in all cases (irrespective of its effect on ganglion cell activity) (Fig. 4), indicating that the diverse effects of the blocker on the ganglion cells are due to its action in the proximal, but not distal retina. Thus, it appears that the endogenous GABA acting through

ionotropic GABA receptors may have an inhibitory as well as an excitatory action on the individual frog ganglion cells and the mode of this action does not depend on the ganglion cell type.

The role played by the GABAergic system in *generation of transient responses* in nonmammalian ganglion cells is a matter of debate. Some authors argue that the GABAergic system is responsible for the transient pattern of responses and its blockade converts the transient responses into sustained ones (Bonaventure et al. 1980; Dong and Werblin 1998; Liu et al. 2007; Roska et al. 2000). There is no agreement among these authors; however, what type of mechanisms (presynaptic or postsynaptic) and GABA receptors is involved in GABA action. Dong and Werblin (1998) have found that picrotoxin, but not bicuculline, converts the transient pattern of the responses into a sustained one, while Roska et al. (2000) reported that bicuculline also increases the duration of the spiking pattern in one-third of the ON–OFF GCs. Thus, Roska et al. (2000) suggest that postsynaptic $GABA_A$ receptors on GCs dendrites take part in the described effect, while Dong and Werblin (1998) argue that only $GABA_C$ receptors located at the bipolar cell terminals are responsible for the effect. The difference between the results of Dong and Werblin (1998) and Roska et al. (2000) obtained in one and same species (tiger salamander) may depend on the measurement techniques; Dong and Werblin (1998) measured voltage in the whole-cell patch mode, while Roska et al. (2000)

measured the spiking output in the ON cell patch mode. The latter allows measuring of the spiking output without decreasing the contribution of inhibition. In contrast to the above cited authors, other authors argue that the GABAergic system is not responsible for the transient pattern of GC spiking. It has been demonstrated that the blockade of GABA$_A$ and GABA$_C$ receptors does not convert the transient responses of GCs to sustained ones in amphibian retina (Bieda and Copenhagen 2000). Bieda and Copenhagen (2000) have found that picrotoxin induces a significant increase in spike count but only small changes in duration of the responses in transient ON GCs. The authors concluded that inhibitory pathways are not required for generation of transient responses, but these pathways do serve to modulate transient ganglion cell spiking responses via inhibitory inputs directly to the ganglion cell. We have shown (Popova et al. 2003) that phasic OFF GCs in frog retina retain the transient character of their discharges under the influence of picrotoxin, although their light responses may be inhibited (4 out of 9 cells) or enhanced (3 out of 9 cells) by the blocker. We have demonstrated, however, that picrotoxin can influence the temporal aspects of light-evoked discharges in some sustained GCs. Some sustained OFF GCs (5 out of 8) appear as transient ones under the influence of picrotoxin, because of great reduction of their tonic component (Fig. 5c). In the other sustained OFF cells, the tonic component was enhanced and the cells retained their sustained manner of spiking during the GABAergic blockade (Fig. 5d). Thus, the endogenous GABA acting on ionotropic GABA receptors can modulate the temporal characteristics of some, but not all sustained frog GCs.

Summary The spiking output of many nonmammalian GCs depends on the activity of endogenous GABA acting through ionotropic GABA receptors. The GABA effects on GC spiking activity could be inhibitory as well as excitatory and the mode of GABA action does not depend on the ganglion cell type (especially in frog retina). There is a good agreement between the results obtained with extracellular GC spike recording (frog, Popova et al. 2003) and those obtained with recording GC synaptic potentials (mudpuppy, Frumkes et al. 1981) in amphibian retina. The role played by GABA, acting through ionotropic GABA receptors, in establishing the transient character of GC discharges is not resolved yet. Solid arguments that support the crucial role of GABA in this process are presented as well as arguments that reject it. The significance of metabotropic GABA receptors in mediating the endogenous GABA action on GC spiking output is not well evaluated in nonmammalian retina.

Effects of GABA and GABA antagonists in mammalian retina

There is no consensus among the authors if GABA influences all types of mammalian GCs or its action possesses ON–OFF or sustained–transient asymmetry. Some authors have found that exogenously applied GABA depresses the spontaneous and light-evoked activity of all ganglion cells irrespective of their physiological type (cat, Straschill and Perwein 1969; Bolz et al. 1985; Müller et al. 1992; rabbit, Ames and Pollen 1969; monkey, McMahon et al. 2004). Consistent with these results are the effects of ionotropic GABA receptor blockade in rabbit retina. It has been shown that picrotoxin increases the spontaneous activity of all types of brisk GCs: sustained and transient, ON and OFF (Ames and Pollen 1969; Caldwell and Daw 1978). The blocker augments also the light-evoked activity of all transient ganglion cells (Ames and Pollen 1969; Caldwell and Daw 1978; Farajian et al. 2011), although the effect is most pronounced on the OFF GCs (Ames and Pollen 1969).

A clear *ON–OFF asymmetry* in the action of GABA and its antagonists has been demonstrated, however, in cat and rodent retinas. In cats, the blockade of *ionotropic* GABA$_A$ *receptors* (by bicuculline) enhances the spontaneous and light-evoked activity of all ON GCs (sustained and transient) (Ikeda and Sheardown 1983; Bolz et al. 1985; Priest et al. 1985; Ikeda et al. 1990; Müller et al. 1992), but it has no effect (Ikeda and Sheardown 1983; Priest et al. 1985) or even suppresses (Ikeda et al. 1990; Müller et al. 1992; Saito 1981, 1983) the activity of the most OFF GCs. Blockade of both GABA$_A$ and GABA$_C$ receptors (by picrotoxin) also increases the responses of transient ON GCs and decreases that of transient OFF GCs (Frishman and Linsenmeier 1982). All these results indicate that the ON GCs, but not the OFF GCs, are under tonic and light-evoked inhibitory GABAergic influences mediated by ionotropic GABA receptors in cat retina. The activity of OFF GCs is suppressed during the GABAergic blockade, because bicuculline disinhibits glycinergic amacrine cells, which in turn increase their inhibition onto OFF GCs (Müller et al. 1992). This inhibitory action of bicuculline is seen only at lower stimulus contrasts, while at higher contrasts the discharges of OFF GCs are even enhanced (Bolz et al. 1985). Some authors argue, however, that the described ON–OFF asymmetry in GABA action is seen only in central, but not peripheral cat retina (Priest et al. 1985). In retinal periphery, GABA inhibits and bicuculline excites both the ON and OFF GCs, leading to the suggestion that GABA receptors are present upon only the ON cells in the area centralis, but upon both the ON and OFF cells in retinal periphery (Priest et al. 1985). The latter suggestion is not confirmed by other authors. ON–OFF asymmetry, opposite to that described for the action of ionotropic GABAergic agents, has been reported for the action of *metabotropic GABA receptor* agents in cat retina. Antagonists of GABA$_B$ receptors (phaclofen and 2-hydroxy-saclofen) increase the maintained activity of sustained OFF GCs, but reduce the

maintained activity of sustained ON GCs, while baclofen has opposite effects (Ikeda et al. 1990; Müller et al. 1992). The antagonists of GABA$_B$ receptors markedly increase also the light-evoked firing of OFF GCs irrespectively of their sustained or transient subtype (Ikeda et al. 1990; Müller et al. 1992), while they lightly reduce the light-driven spiking of sustained ON GCs (Ikeda et al. 1990). The inhibitory action upon the ON GCs is seen only during low-contrast stimulation, while during high-contrast stimulation the spiking of the ON GCs is even enhanced (Müller et al. 1992). What kind of GABA receptors mediates the action of endogenous GABA on cat GCs is a matter of debate. Müller et al. (1992) proposed that the effects of GABA are mediated mainly by GABA$_A$ receptors, while Ikeda et al. (1990) argue that both GABA$_A$ and GABA$_B$ receptors are involved. The latter authors suggest that the GABA$_A$ action predominates in cat ON GCs, while the GABA$_B$ action predominates in cat OFF GCs.

ON–OFF asymmetry in the action of GABA has been demonstrated also in rodent retina. Sagdullaev et al. (2006) have found that the spontaneous and light-evoked activity of the ON, but not OFF GCs, is augmented in GABA$_C$R knockout mice. This is true for both sustained and transient cell types. It is apparent that the ON–OFF asymmetry of GABA action, mediated by ionotropic GABA receptors in mice, is opposite to that described in cats. Sagdullaev et al. (2006) have found also that the dynamic range of ON GCs responses in GABA$_C$ receptor knockout mice is significantly reduced compared to wild-type mice and it becomes comparable to that of OFF GCs in wild-type mice. This result suggests that GABA$_C$ receptor-mediated inhibition normally extends the dynamic range of visually evoked increment, but not decrement responses. The latter suggestion is not supported by the results of Jensen (2012) in rat retina. He has found that blocking of GABA$_C$ receptors by TPMPA slightly reduces the responses of ON GCs to light flashes, except for flashes of high intensity, which were unaltered. Thus, the blocker decreases the light sensitivity of the responses, while the dynamic operating range and the maximum peak response of the ON GCs remain unaltered. The author did not comment the blocker's effects on the OFF GCs. The difference in the findings of the two studies in rodents (Sagdullaev et al. 2006 and Jensen 2012) may originate in different manner of analysis of the light responses of GCs. While Sagdullaev et al. (2006) include the sustained response in their analysis (in a 1 s window), Jensen (2012) analyzes only the transient component of the response (in a 100 ms window). In line with the findings of Sagdullaev et al. (2006) are the results of Nirenberg and Meister (1997), who reported that picrotoxin increases the peak and average firing rate of transient ON GCs and often reveals a second more extended phase, which remains separated from the main ON discharge.

Some authors argue that the action of GABA and its antagonists shows *transient-sustained*, but not ON–OFF *asymmetry* in cat retina. Kirby and Enroth-Cugell (1976) have found that GABA and ionotropic GABA receptor antagonists (picrotoxin and bicuculline) modulate the activity of transient GCs, but they have no effect on the sustained GCs. Picrotoxin and bicuculline suppress the responses of all transient GCs irrespective of their ON or OFF subtype with the effect being stronger for the lower than higher stimulus intensities. Similarly, Saito (1981, 1983) reported that bicuculline has no effect on the sustained ON GCs, while it affects the surround response of the transient ON GCs. The cause for the conflicting results obtained in cat retina may be the different manners of blocker application and different conditions of light adaptation. Kirby and Enroth-Cugell (1976) and Frishman and Linsenmeier (1982) have used in vivo systemic application of blockers under scotopic (Kirby and Enroth-Cugell 1976) or high mesopic and photopic (Frishman and Linsenmeier 1982) conditions. Saito (1981, 1983) applied them to the bathing medium in isolated eyecup preparations under low mesopic conditions, while Bolz et al. (1985), Ikeda and Sheardown (1983) and Priest et al. (1985) applied them iontophoretically in the intact eyes in vivo under mesopic (Bolz et al. 1985; Müller et al. 1992; Frumkes et al. 1995) and photopic conditions (Bolz et al. 1985; Ikeda and Sheardown 1983; Priest et al. 1985). It is known that in mammalian retina the rod and cone pathways differ in some aspects (review: Dowling 2012), which could account for the differences in the GABA effects obtained under scotopic and photopic conditions of illumination.

The role of endogenous GABA in response shaping of primate ganglion cells is largely unknown. McMahon et al. (2004) have observed that the effect of picrotoxin on response amplitude of parasol ganglion cells varies from cell to cell, with most cells being attenuated. More studies are needed to establish the significance that the GABAergic system has for the ganglion cell functioning in primate retina.

There remains some controversy as to whether the GABAergic system participates in *generation of transient responses* in mammalian ganglion cells. It appears that GABA acting through *ionotropic* GABA *receptors* truncates the GC responses in rabbits, while it extends the duration of GC responses in cats. It has been shown that the blockade of ionotropic GABA receptors (by picrotoxin) in rabbits enhances and prolongs transients in the response to diffuse light and even causes some ON sluggish-transient cells to resemble the ON sluggish-sustained cells in their response to a central spot (Caldwell and Daw 1978). Opposite results have been reported in cat retina, where the responses of all GCs irrespective of their subtype become considerably more transient during the treatment with

picrotoxin or bicuculline (Müller et al. 1992; Frumkes et al. 1995). The responses of OFF ganglion cells are affected to a greater degree than that of the ON GCs. These findings imply that endogenous activation of ionotropic GABA receptors acts to extend the duration of discharges in both the ON and OFF cat GCs. Other authors argue, however, that the effects of ionotropic GABA receptor antagonists in cat retina depend on the GC type. It has been shown that the GABA_A receptor blockade can influence in an opposite manner the duration of the ON and OFF discharges. Bicuculline makes the responses of ON GCs more sustained, while it reduces the sustained component in the OFF responses and makes them more transient (Ikeda and Sheardown 1983; Bolz et al. 1985). The transient peaks in the OFF responses may be unaltered (Ikeda and Sheardown 1983) or increased during bicuculline treatment (Bolz et al. 1985). Why bicuculline makes the responses of cat ON GCs more transient in some studies (Frumkes et al. 1995; Müller et al. 1992), but more sustained in other ones (Bolz et al. 1985; Ikeda and Sheardown 1983) is difficult to be explained, because all the authors applied the blocker iontophoretically in vivo.

The role played by *metabotropic GABA receptors* in modulating the temporal characteristics of GC discharges is investigated only in cat retina. It has been shown that baclofen suppresses the tonic component of the discharges of both the ON and OFF GCs leaving the peak unchanged or even enhanced (Müller et al. 1992). Thus, the light responses of the cells become more phasic during baclofen treatment. Müller et al. (1992) could not determine whether baclofen acts on GABA_B receptors located postsynaptically or presynaptically, but the authors think "that its effects are due to both actions". The action of GABA_B receptor antagonists (phaclofen, saclofen) is opposite to that of baclofen. They enhance the tonic component of OFF GC discharges (Ikeda et al. 1990; Müller et al. 1992), while their phasic component may be enhanced (Müller et al. 1992) or suppressed (Ikeda et al. 1990). Thus, it appears that endogenous activation of metabotropic GABA receptors acts to truncate the discharges of OFF GCs in cat retina, which is opposite to GABA action mediated through ionotropic GABA receptors.

The participation of the GABAergic system in the inhibitory interactions between the ON and OFF channels at ganglion cell level will not be discussed here, because it is subject of future review. An interesting observation in both the rabbit and mouse retinas is that the blockade of ionotropic GABA receptors (by picrotoxin) unmasks a robust OFF response in transient ON GCs and a robust ON response in transient OFF GCs, indicating that mammalian ganglion cells receive masked excitatory crossover inputs (Nirenberg and Meister 1997; Roska and Werblin 2001; Farajian et al. 2011). Similar results have been

demonstrated in frog retina (Popova et al. 2003) (Fig. 5), suggesting that masking of excitatory crossover inputs caused by GABA is common feature of vertebrate retina. It has been proposed that feedback inhibition, mediated by both GABA_A and GABA_C receptors (Farajian et al. 2011) or only GABA_C receptors (Roska and Werblin 2001) and not feedforward inhibition, is responsible for masking of opposite polarity response in ganglion cells.

Summary The action of endogenous GABA on GC spiking activity shows some species-specific differences in mammalian retina. The GABAergic system influences the discharges of all GC types in rabbit retina, which is consistent with the results obtained by recording IPSPs and EPSPs in different types of rabbit GCs. The action of endogenous GABA appears to possess ON–OFF asymmetry in cats and rodents. However, the ON–OFF asymmetry of GABA action mediated by ionotropic receptors in cats is opposite to that in rodents. An opposite ON–OFF asymmetry is demonstrated also for the GABA action mediated by ionotropic vs. metabotropic receptors in cat retina. In all these cases, GABA acts to diminish one of the responses and to enhance the other (especially at lower stimulus contrasts). The described ON–OFF asymmetry of GABA action in cats is call in question, however, by some authors that argue that GABA action possesses only transient-sustained asymmetry. The role that the GABAergic system plays in generation of the transient GC spiking in mammalian retina is not yet fully understood. Some data indicate that the endogenous GABA may influence in an opposite manner the duration of GC discharges in different mammalian species (rabbits vs. cats) as well as the ON vs. OFF discharges in one and same species (cat). It appears that both ionotropic and metabotropic GABA receptors are involved in temporal tuning of cat GC responses, but their activation leads to opposite changes in GC discharge duration.

Effects on receptive fields

The effect of GABA on the receptive fields of ganglion cells appears to fall into two groups. In the first group, GABA seems to be involved in the formation of the ganglion cell receptive field surround, whereas in the second group GABA seems to be involved in the trigger features formation of complex ganglion cells.

Effects on centre-surround organization

In *nonmammalian retina,* the significance of the GABAergic neurotransmission for the centre-surround organization of ganglion cell receptive fields has been investigated mainly in amphibians. There is agreement among the authors that endogenous GABA mediates the inhibition exerted by the surround upon the centre of ganglion cell

receptive field. It has been shown that the blockade of ionotropic GABA receptors (by picrotoxin) causes a marked enhancement in the sensitivity for the large test spots and an increase in the size of the receptive field of all cell classes studied (frog, Bonaventure et al. 1980; Bonaventure and Wioland 1981; Backstrom 1981; tiger salamander, Cook and McReynolds 1998). Thus, after application of the blocker the area threshold curve shows no lateral inhibition, indicating that it is due to the GABAergic inhibition. Some authors argue, however, that GABA mediates the suppressive effect of dim, but not bright surround upon the centre excitatory response (Ichinose and Lukasiewicz 2005). It has been shown that the $GABA_C$, but not $GABA_A$ receptor blockade, eliminates the suppressive effect of dim surround illumination upon the centre-evoked EPSCs in tiger salamander retina. On the other hand, the $GABA_C$ receptor blockade alone and in combination with $GABA_A$ and $GABA_B$ receptor blockade have no effect on the bright surround inhibition of ganglion cell EPSPs, indicating that different lateral inhibitory pathways mediate the effects of dim and bright surround illumination observed in cone-driven ganglion cells. The former is GABA dependent, suggesting that it is mediated by the inner plexiform layer, while the latter is not GABA dependent, but carbenoxolone- and cobalt-sensitive, suggesting that it is mediated by the outer plexiform layer.

In *mammalian retina,* the effects of ionotrtopic GABA receptor antagonists on the centre-surround organization of ganglion cell receptive fields have been investigated mainly in rabbits, cats and monkeys. There is no consensus among the authors if the GABAergic system plays a role in centre-surround organization of all rabbit GCs or its action possesses transient-sustained asymmetry. Some authors have demonstrated that picrotoxin changes the centre-surround balance in favor of the centre for transient cells, but not for sustained cells irrespective of their subtype (brisk or sluggish) (Caldwell and Daw 1978). Other authors, however, argue that the GABAergic mechanisms contribute to the surround inhibition of brisk-sustained GCs as well (Buldyrev and Taylor 2013). Buldyrev and Taylor (2013) have found that combined $GABA_A$ and $GABA_C$ receptor blockade (with TPMPA plus SR95531) decreases the surround inhibition in ON GCs to the same extent as isolated $GABA_C$ blockade (by ~25 %), while it causes an additional inhibition in OFF GCs (from 9 to 17 %). The authors concluded that the GABAergic system mediates the surround inhibition in sustained ON and OFF GCs through presynaptic mechanisms, which involve $GABA_C$ receptors for ON GCs and both $GABA_A$ and $GABA_C$ receptors for OFF GCs. The GABAergic system is involved also in centre-surround organization of receptive fields in rabbit ganglion cells with trigger features. It has been shown that the pharmacological blockade of both $GABA_A$ and $GABA_C$ receptors

(with SR95531 plus TPMPA) eliminates the suppression of centre excitatory currents by stimulation of the entire surround of local edge detectors (Russell and Werblin 2010). Because the authors have used inverting gratings in the surround with 50 μ stripe sizes, which do not stimulate horizontal cells, they concluded that a GABAergic feedback inhibition of bipolar cell terminals is responsible for the centre-surround antagonism. They presented data suggesting that feedback inhibition to the OFF bipolar cells is mediated more by $GABA_A$ receptors (with a smaller role of $GABA_C$ receptors), while feedback inhibition to the ON bipolar cells is mediated by both $GABA_A$ and $GABA_C$ receptors. Thus, it appears that the surround inhibition is mediated by different proportions of GABA receptors in rabbit-sustained GCs vs. rabbit local edge detectors.

The involvement of the GABAergic system in centre-surround organization of cat ganglion cell receptive fields is a matter of debate. Some authors argue that the GABAergic system takes part in it (Kirby and Enroth-Cugell 1976; Kirby 1979; Ikeda and Sheardown 1983), other authors reject this possibility (Bolz et al. 1985; Frishman and Linsenmeier 1982) and still other authors suggest that the GABAergic participation depends on the photoreceptor input (Kirby and Schweitzer-Tong 1981a, b). Involvement of the GABAergic system in centre-surround organization of GC receptive fields is supported by data showing that the blockade of ionotropic GABA receptors (by picrotoxin or bicuculline) causes a shift of the center-surround balance in favor of the centre (Kirby and Enroth-Cugell 1976; Kirby 1979; Ikeda and Sheardown 1983). Contradiction exists, however, about the type of GCs affected. Some authors have found that picrotoxin and bicuculline cause such a shift in transient ON and OFF cells (Kirby and Enroth-Cugell 1976; Kirby 1979), while other authors reported that bicuculline affects centre-surround balance of the ON, but not OFF GCs irrespective of their subtype (Ikeda and Sheardown 1983). Involvement of the GABAergic system in centre-surround organization of GC receptive fields is call in question by findings indicating that the action of bicuculline shows no difference with respect to centre and surround stimulation in all GCs irrespective of their ON, OFF, sustained or transient type (Bolz et al. 1985). Bicuculline does not change also the form of the area-response curve, indicating that the receptive field centre size remains the same. These results suggest that $GABA_A$ receptors do not mediate the inhibitory surround response. Similar results have been obtained with application of picrotoxin that blocks both $GABA_A$ and $GABA_C$ receptors (Frishman and Linsenmeier 1982). Picrotoxin causes no changes in centre and surrounds sensitivity and their sizes in both ON and OFF transient GCs under mesopic and photopic conditions of stimulation (Kirby and Schweitzer-Tong 1981a, b; Frishman and Linsenmeier 1982). However, picrotoxin

decreases the equivalent centre diameter of transient ON GCs and increases it in the transient OFF GCs under scotopic conditions of adaptation (Kirby and Schweitzer-Tong 1981a, b). The latter results suggest that the action of endogenous GABA on the centre summation area of ganglion cell receptive fields depends on the type of the photoreceptor input (cones or rods) as well as on the subtype of the ganglion cells (ON or OFF).

The participation of the GABAergic system in centre-surround organization of primate ganglion cell receptive fields is not well evaluated. It has been found that picrotoxin does not eliminate the center-surround structure of blue ON color-opponent ganglion cells (Crook et al. 2009) and it does not alter centre-surround balance of parasol GCs under photopic conditions of illumination (McMahon et al. 2004). However, what is its action under dim surround illumination is largely unknown.

Summary Endogenous GABA mediates the inhibition exerted by the surround upon the centre of ganglion cell receptive field independently of the GC type in amphibian retina. This action of GABA is mediated by $GABA_C$ receptors and it is evident under conditions of dim, but not bright surround illumination. The involvement of the GABAergic system in centre-surround organization of GC receptive fields in mammalian retina appears to posses some species-specific differences. Most of the data indicate that in rabbits GABA mediates the surround antagonism in different types of GCs. Its action is mediated through different proportions of $GABA_A$ and $GABA_C$ receptors in sustained GCs vs. local edge detectors. In cats, the participation of the GABAergic system in centre-surround organization of retinal GCs is a matter of debate. It is not well understood if the endogenous GABA influences the surround inhibition of all GC types or its action possesses ON–OFF or sustained-transient asymmetry. Some data indicate that GABA action in cat retina may depend on the level of surround illumination in a way similar to that described in amphibian retina.

Effects on trigger features

There is agreement among the authors that the GABAergic system contributes to feature-related activity of retinal ganglion cells. It has been shown that the blockade of ionotropic GABA receptors (by picrotoxin or bicuculline) makes the complex receptive fields simpler and thus eliminates their trigger features (rabbit, Caldwell et al. 1978; fish, Lasater and Lam 1984). Bicuculline abolishes the anisotropies of spatial receptive field of ON, but not OFF GCs, so they resemble "bipolar-like" spatial fields (Lasater and Lam 1984). Picrotoxin eliminates the orientation specificity of orientation sensitive cells, and it changes the bar-flank arrangement of the receptive field into a centre-surround

arrangement, indicating that the orientation specificity is due to inhibitory rather than excitatory mechanisms (Caldwell et al. 1978). Large field cells (which normally do not response to slow movement) are converted to normal transient cells under the influence of picrotoxin, because the cells begin to response to fast and much better to slow speeds (Caldwell et al. 1978). Uniformity detectors are cells with moderately high rate of spontaneous activity, which is inhibited by all stimuli irrespective of their shape, contrast, size, movement, etc. Picrotoxin eliminates their centre and surround inhibition, so they begin to respond with sustained ON response during diffuse light illumination (Caldwell et al. 1978).

Involvement of the GABAergic system in creating the directional selectivity of direction selective GCs has been subject of numerous studies. Direction selective ON and ON–OFF ganglion cells respond strongly to motion in a preferred direction and weakly to motion in the opposite, null direction. The mechanisms and circuitry underlying directional selectivity are still not fully understood. Directional selectivity can be created by two principal synaptic mechanisms: (1) direction selective release of inhibitory neurotransmitter (GABA) during null direction motion and (2) direction selective release of excitatory neurotransmitter during preferred direction motion. It is not resolved yet how each of these mechanisms contributes to the directional selectivity of GCs in different species. In amphibian retina, their contributions may depend on GC type. It has been shown that the directional selectivity is created by modulating the excitatory input only in frog ON and OFF direction selective GCs (because these cells receive no detectable inhibitory input), while it is created by modulating both the excitatory and inhibitory inputs in ON–OFF GCs (Watanabe and Murakami 1984).

In mammalian retina, the GABAergic starburst amacrine cells are a key component in the direction selective circuit (reviews: Demb 2007; Zhou and Lee 2008; Borst and Euler 2011; Werblin 2011). These cells exert spatially offset GABAergic inhibition to ganglion cells, because starburst amacrine cells located on the null side of a ganglion cell provide significantly stronger inhibition than starburst amacrine cells located on its preferred side (rabbit, Fried et al. 2002; Lee et al. 2010; mouse, Wei et al. 2011). It has been shown that the establishment of direction selective circuits during development is mediated by an asymmetrical increase in the strength of the unitary $GABA_A$ receptor-mediated conductance between starburst amacrine cells and direction selective GCs (Wei et al. 2011). Wei et al. (2011) could not determine, however, the relative role that increases in synapse number versus synapse strength have in the increase in the unitary GABA conductance in the synapses between null side starburst amacrine cells and direction selective GCs. How synapses between starburst

amacrine cells and direction selective GCs are organized to provide asymmetric inhibition is not fully understood, because no apparent asymmetry is detected in the morphology or the distribution of synaptic markers in both cell types as well as in the density of contacts and cofasciculations between distal starburst amacrine cell processes and dendrites of direction selective GC (Famiglietti 2002; Jeon et al. 2002; Chen and Chiao 2008; Wei et al. 2011). Recently, however, when statistical analysis of contacts between the two cell types has been made for the first time in mouse retina, a structural asymmetry has been discovered (Briggman et al. 2011). It has been shown that a direction selective GC receives the great majority of starburst amacrine cell synapses from dendrites that roughly point in the ganglion cell's null direction. The probability for a synaptic contact is higher when the local angle of starburst amacrine cell dendrite closely matches the ganglion cell null direction. It remains to be determined if similar structural asymmetry exists in other mammalian retinas. Many data indicate that the release of GABA from each dendritic branch of starburst amacrine cells is also directionally selective (reviews: Demb 2007; Borst and Euler 2011). It is stronger for centrifugal than for centripetal stimulus movement (Euler et al. 2002; Lee and Zhou 2006). In addition, excitation of direction selective GCs in response to null direction movement is reduced by inhibitory signal acting at a site that is presynaptic to the cell (Fried et al. 2002). Thus, the preferred direction evokes a large excitatory conductance followed by a small inhibitory conductance, while the null direction evokes a small excitatory conductance that coincides with a large inhibitory conductance (review: Demb 2007). According to the working model presented by Demb (2007), each point on the dendritic tree of direction selective GCs receives excitatory input (from bipolar cells), strongest for motion in the preferred direction, and inhibitory input (from starburst amacrine cells), strongest for motion in ganglion cell's null direction. The integration of these direction selective synapses would then be amplified by local voltage-gated Na^+ channels that generate dendritic action potentials when light bars are moved in a preferred, but not null direction (Sivyer and Williams 2013). The interplay of all these components ensures a robust directional selectivity in the spiking responses of direction selective GCs.

It has been shown that ionotropic GABA receptor antagonists abolish the directional sensitivity of direction selective ganglion cells, so that the cells response more equally to stimuli moving in the preferred and null directions (turtle, Ariel and Adolph 1985; rabbit, Wyatt and Daw 1976; Caldwell et al. 1978; Ariel and Daw 1982; Kittila and Massey 1995; Chiao and Masland 2002; Ackert et al. 2006). The response onset time for movement in the null direction is dramatically shorter during picrotoxin application,

resulting in equivalent onset latencies in response to both preferred and null stimulation (Ariel and Daw 1982; Chiao and Masland 2002; Ackert et al. 2006). Thus, it appears that GABA is inhibitory transmitter likely to mediate lateral inhibition in the null direction. Application of picrotoxin also restores the synchronized spiking of ON direction selective cell pairs during null stimulation, indicating that GABAergic inhibition associated with stimulus movement in the null direction underlies the desynchronized firing between neighboring ON direction selective cells (Ackert et al. 2006). The detection of null stimulus movement appears a key to the directional selectivity of ON direction selective cells, evoking both an attenuation of spike frequency and a desynchronization of neighbors. Ackert et al. (2006) posit that active desynchronization reduces summation of synaptic potentials at target cells and thus provides a secondary mechanism by which ON direction selective cell ensembles can signal direction of stimulus motion to the brain. There may be, however, some species-specific differences in picrotoxin effects on direction selective ganglion cells. Application of picrotoxin results in appearance of responses to both leading and trailing edges of moving spots in turtle OFF direction selective cells (Ariel and Adolph 1985), while the blocker has no such effect in ON direction selective cells in rabbit retina (Caldwell et al. 1978). The effects of GABA on direction selective GCs in rabbit retina are probably mediated by $GABA_A$ receptors, because specific $GABA_A$ receptor antagonists (SR-95531, bicuculline) abolish directionally selective responses from ON and ON–OFF GCs (Kittila and Massey 1995; Fried et al. 2005) and they do this in much lower concentrations than picrotoxin (Massey et al. 1997).

The GABAergic system not only mediates the lateral inhibition in null direction, but it modulates the excitatory input to direction selective GCs as well. It has been shown that the $GABA_A$ receptor blockade increases both the spatial extent of excitatory receptive field of direction selective cells and the magnitude of excitatory input to them. The latter is mediated by glutamate and acetylcholine and its directional selectivity is lost during $GABA_A$ receptor blockade (Fried et al. 2005). Fried et al. (2005) suggest that the null direction suppressions that shape the glutamatergic and cholinergic excitatory inputs are mediated by synaptic pathways that culminate at $GABA_A$ receptors. Park et al. (2014) also argue that GABA acting on $GABA_A$ receptors is the apparent sole source of directional selective input onto ON–OFF direction selective GCs in mouse retina. They have found that with $GABA_A$ receptors blocked the excitatory currents to direction selective GCs lack directional selectivity. Involvement of $GABA_A$ receptors is supported also by data, showing that there is significant impairment of directional selective responses of GCs and dramatic drop in the proportion of cells exhibiting

directional selective phenotype in both the ON and ON–OFF populations in GABA$_A$ receptor knockout mice compared to wild-type mice (Auferkorte et al. 2012).

Some studies indicate, however, that the endogenous GABA acting on ionotropic GABA receptors is not the sole source of directional selective inputs to direction selective GCs. Studies of rabbit and turtle retinas indicate that after application of picrotoxin, some of the ON–OFF direction selective ganglion cells still show directional selective responses, but often with reverse preference (turtle, Smith et al. 1996; rabbit, Grzywacz et al. 1997). Under picrotoxin, directional selectivity was lost in 33 % of the rabbit and 21 % of turtle OFF direction selective cells regardless of stimulus contrast and speed. In most other cells, loss, maintenance, or even reversal of preferred and null directions could occur as speed and contrast are modulated. In GABA$_A$ receptor knockout mice with additional GABA$_A$ and GABA$_C$ receptor blockade, Auferkorte et al. (2012) still observed cells with high directional selectivity index, indicating that other factors contribute strongly to their directional selectivity. The authors proposed that "asymmetric dendritic morphology and/or active dendritic properties provide sufficient directional tuning in at least some direction selective GCs". Similar results have been reported in amphibian retina, where application of picrotoxin reduces the directional selectivity in about half of the cells (tiger salamander, Pan and Slaughter 1991). Pan and Slaughter (1991) have shown that baclofen (GABA$_B$ receptor agonist) enhances the normal directional responses in some neurons and induces directional selective responses in about 30 % of the cells that are not normally directional. Their results indicate that activation of GABA$_B$ receptors could induce directional selectivity in GCs. Picrotoxin suppresses directionality in about half of the induced directional cells (similarly to normal directional cells), while a combination of picrotoxin and strychnine almost always suppresses directionality. The authors propose that glycine could have a role in the formation of amphibian directional responses, but they do not test strychnine alone to evaluate this hypothesis.

Interestingly, application of picrotoxin reveals an OFF response in ON direction selective ganglion cells, which remains after ON channels blockade, indicating that it is generating by the OFF pathway (Ariel and Daw 1982; Ackert et al. 2009). This OFF response is directional selective, but, surprisingly, its preferred direction is opposite to that of the ON response of the same cell (Ackert et al. 2009). It is abolished by application of a gap junction blocker, suggesting that it arises from electrical synapses between ON direction selective cells and neighboring polyaxonal amacrine cells, which receive excitatory signals through chemical synapses with OFF bipolar cells and OFF starburst amacrine cells. Ackert et al. (2009) suggest that under certain stimulus conditions, the GABAergic inhibition is relieved so that the OFF signals are incorporated in the spike code of ON direction selective cells to affect optokinetic signaling.

Ionotropic GABA receptor antagonists affect also some other properties of direction selective ganglion cells in addition to directional selectivity. It has been shown that picrotoxin eliminates the size specificity of direction selective GCs so that they respond equally to narrow and wide moving bars (Wyatt and Daw 1976; Caldwell et al. 1978; Ariel and Daw 1982). During picrotoxin application, the ON and ON–OFF direction selective cells respond better to all speeds of stimulus motion, indicating that the GABAergic inhibition may also be involved in velocity tuning of direction selective cells (Wyatt and Daw 1976; Caldwell et al. 1978; Ariel and Daw 1982; Ariel and Adolph 1985).

Summary The GABAergic system takes part in creating the directional selectivity of GCs in both nonmammalian and mammalian retina. It mediates the lateral inhibition in the null direction movement and contributes for the directional selectivity of excitatory inputs to direction selective GCs. These effects of GABA are probably mediated by GABA$_A$ receptors, although activation of GABA$_B$ receptors could also contribute to the directional selectivity of amphibian GCs. It appears, however, that GABA is not the sole source of directional selective input to GCs. What other factors contribute to directional selectivity of retinal GCs remain to be determined.

Conclusion

Many aspects of GABA action on retinal ganglion cells are well evaluated. It is known that the GABAergic neurotransmission is essential for shaping the light-evoked responses in great number of ganglion cells. Blocking this transmission in the retina may increase, but also inhibit ganglion cell activity and the mode of this action does not depend on the ganglion cell type, especially in nonmammalian retina. It is also known that GABA plays a crucial role in establishing the directional selectivity of complex ganglion cells. It is still not resolved yet if the action of endogenous GABA possesses ON–OFF and sustained-transient asymmetry in both nonmammalian and mammalian retina. What is the function of different types of GABA receptors in mediating GABA action on ganglion cells is an open question that needs further examination. The same is true for the participation of the GABAergic neurotransmission in transient response generation of third-order retinal neurons in different vertebrate species.

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