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Glutamate and Glutamate Receptors in the Vertebrate Retina

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General Overview of Synaptic Transmission

Cells communicate with each other electrically, through gap junctions, and chemically, using neurotransmitters. Chemical synaptic transmission allows nerve signals to be exchanged between cells that are electrically isolated from each other. The chemical messenger, or neurotransmitter, provides a way to send the signal across the extracellular space, from the presynaptic neuron to the postsynaptic cell. The space is called a **cleft** and is typically more than 10 nanometers across. Neurotransmitters are synthesized in the presynaptic cell and stored in vesicles in presynaptic processes, such as the axon terminal. When the presynaptic neuron is stimulated, calcium channels open, and the influx of calcium ions into the axon terminal triggers a cascade of events leading to the release of neurotransmitter. Once released, the neurotransmitter diffuses across the cleft and binds to receptors on the postsynaptic cell, allowing the signal to propagate. Neurotransmitter molecules can also bind onto presynaptic autoreceptors and transporters, regulating subsequent release and clearing excess neurotransmitter from the cleft. Compounds classified as neurotransmitters have several characteristics in common (reviewed in Massey (1) and Erulkar (2)).

Briefly: 1) the neurotransmitter is synthesized, stored, and released from the presynaptic terminal; 2) specific neurotransmitter receptors are localized on the postsynaptic cells; and 3) there exists a mechanism to stop neurotransmitter release and clear molecules from the cleft. Common neurotransmitters in the retina are glutamate, GABA, glycine, dopamine, and acetylcholine. Neurotransmitter compounds can be small molecules, such as glutamate and glycine, or large peptides, such as vasoactive intestinal peptide (VIP). Some neuroactive compounds are amino acids, which also have metabolic functions in the presynaptic cell.

Glutamate (Fig. 1) is believed to be the major excitatory neurotransmitter in the retina. In general, glutamate is synthesized from ammonium and α-ketoglutarate (a component of the Krebs cycle) and is used in the synthesis of proteins, other amino acids, and even other neurotransmitters (such as GABA) (3). Although glutamate is present in all neurons, only a few are glutamatergic, releasing glutamate as their neurotransmitter. Neuroactive glutamate is stored in synaptic vesicles in presynaptic axon terminals (4). Glutamate is incorporated into the vesicles by a glutamate transporter located in the vesicular membrane. This transporter selectively accumulates glutamate through a sodium-independent, ATP-dependent process (4-6), resulting in a high concentration of glutamate in each vesicle. Neuroactive glutamate is classified as an excitatory amino acid (EAA), because glutamate binding onto postsynaptic receptors typically stimulates, or depolarizes, the postsynaptic cells.

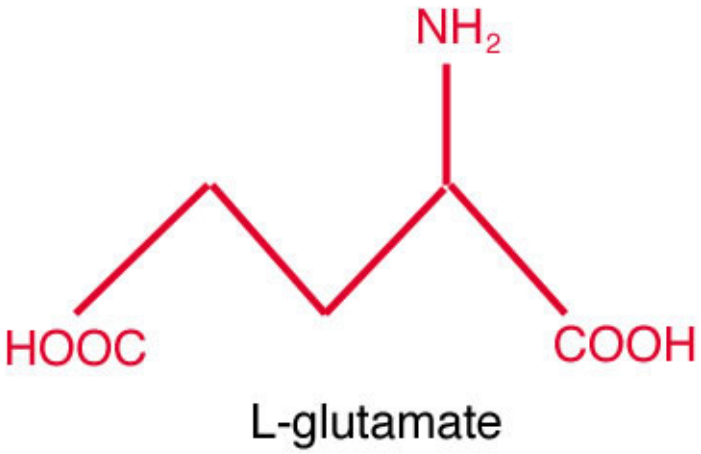

Figure 1. Structure of the glutamate molecule.

Histological Techniques Identify Glutamatergic Neurons

Using immunocytochemical techniques, neurons containing glutamate are identified and labeled with a glutamate antibody. In the retina, photoreceptors, bipolar cells, and ganglion cells are glutamate immunoreactive (7-12) (Fig. 2). Some horizontal and/or amacrine cells can also display weak labeling with glutamate antibodies (7, 8, 10, 13). These neurons are believed to release GABA, not glutamate, as their neurotransmitter (14), suggesting that the weak glutamate labeling reflects the pool of metabolic glutamate used in the synthesis of GABA. This has been supported by the results from double-labeling studies using antibodies to both GABA and glutamate; glutamate-positive amacrine cells also label with the GABA antibodies (8, 13).

Photoreceptors, which contain glutamate, actively take up radiolabeled glutamate from the extracellular space, as do Muller cells (Fig. 3) (15, 16). Glutamate is incorporated into these cell types through a high-affinity glutamate transporter located in the plasma membrane. Glutamate transporters maintain the concentration of glutamate within the synaptic cleft at low levels, preventing glutamate-induced cell death (17). Although Muller cells take up glutamate, they do not label with glutamate antibodies (8). Glutamate incorporated into Muller cells is rapidly broken down into glutamine, which is then exported from glial cells and incorporated into surrounding neurons (18). Neurons can then synthesize glutamate from glutamine (18, 19).

Thus, histological techniques are used to identify potential glutamatergic neurons by labeling neurons containing glutamate (through immunocytochemistry) and neurons that take up glutamate (through autoradiography). To determine whether these cell types actually release glutamate as their neurotransmitter, however, the receptors on postsynaptic cells have to be examined.

Glutamate Receptors

Once released from the presynaptic terminal, glutamate diffuses across the cleft and binds onto receptors located on the dendrites of the postsynaptic cell(s). Multiple glutamate receptor types have been identified. Although glutamate will bind onto all glutamate receptors, each receptor is characterized by its sensitivity to specific glutamate analogs and by the features of the glutamate-elicited current. Glutamate receptor agonists and antagonists are structurally similar to glutamate (Fig. 4), which allows them to bind onto glutamate receptors. These compounds are highly specific and, even in intact tissue, can be used in very low concentrations because they are poor substrates for glutamate uptake systems (20, 21).

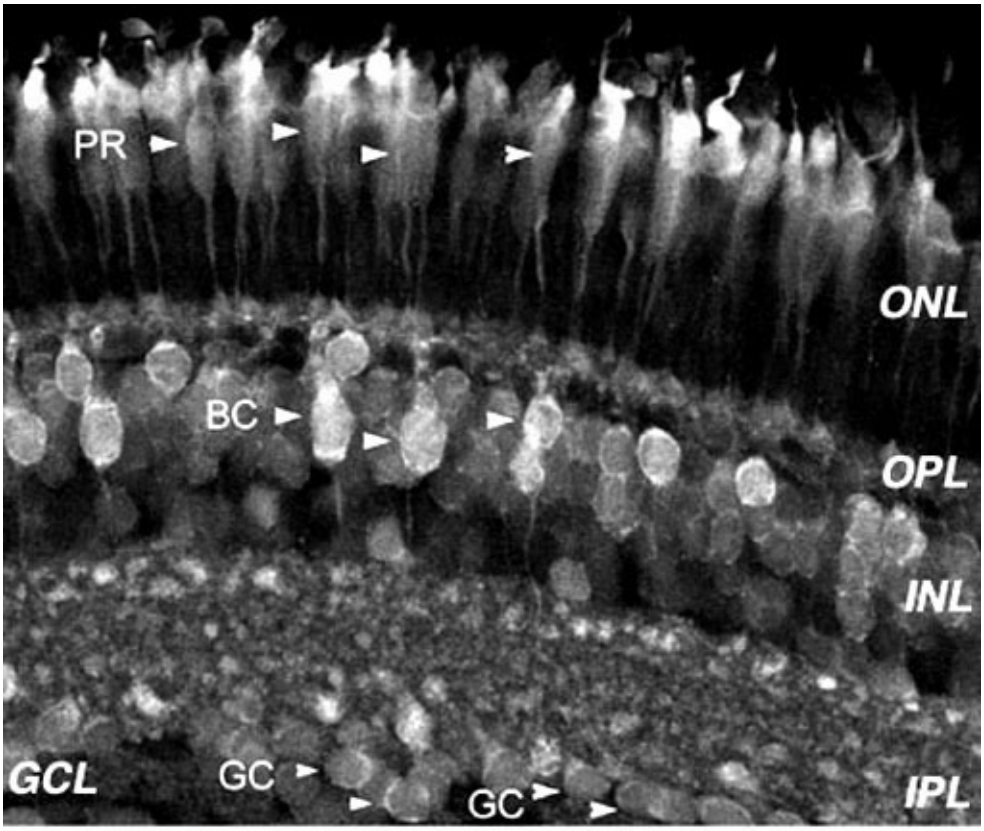

Figure 2. Glutamate immunoreactivity.

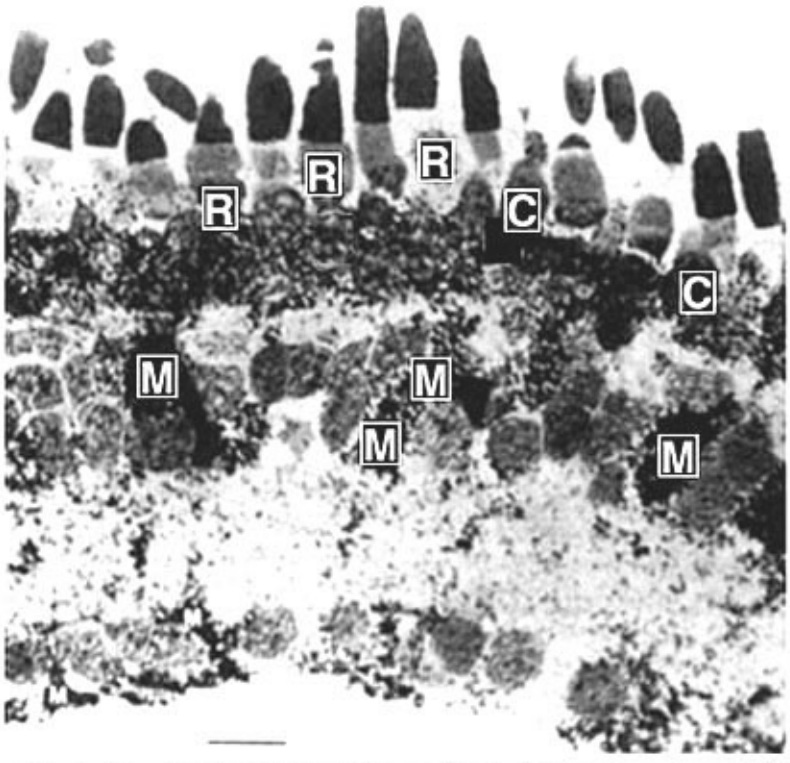

Figure 3. Autoradiogram of glutamate uptake through glutamate transporters.

Two classes of glutamate receptors (Fig. 5) have been identified: 1) ionotropic glutamate receptors, which directly gate ion channels; and 2) metabotropic glutamate receptors, which may be coupled to an ion channel or other cellular functions via an intracellular second messenger cascade. These receptor types are similar in that they both bind glutamate, and glutamate binding can influence the permeability of ion channels. However, there are several differences between the two classes.

Ionotropic Glutamate Receptors

Glutamate binding onto an ionotropic receptor directly influences ion channel activity because the receptor and the ion channel form one complex (Fig. 5a). These receptors mediate fast synaptic transmission between neurons. Each ionotropic glutamate receptor, or iGluR, is formed from the co-assembly of individual subunits. The assembled subunits may or may not be homologous, with the different combinations of subunits resulting in channels with different characteristics (22-26).

Two iGluR types (Fig. 6) have been identified: 1) NMDA receptors, which bind glutamate and the glutamate analog *N*-methyl-D-aspartate (NMDA) and 2) non-NMDA receptors, which are selectively agonized by kainate, AMPA, and quisqualate, but not NMDA.

Non-NMDA Receptors

Glutamate binding onto a non-NMDA receptor opens non-selective cation channels more permeable to sodium (Na^+) and potassium (K^+) ions than calcium (Ca^{2+}) (27). Glutamate binding elicits a rapidly activating inward current at membrane potentials negative to 0 mV and an outward current at potentials positive to 0 mV. Kainate, quisqualate, and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) are the specific agonists at these receptors; CNQX (6-cyano-7-nitroquinoxaline-2,3-dione), NBQX (1,2,3,4-tetrahydro-6-nitro-2,3-dione-benzo[*f*]quinoxaline-7-sulfonamide), and DNQX (6,7-dinitroquinoxaline-2,3-dione) are the antagonists.

In retina, non-NMDA receptors have been identified on horizontal cells, OFF-bipolar cells, amacrine cells, and ganglion cells (see below). Patch clamp recordings (28-32) indicate that AMPA, quisqualate, and/or kainate application can evoke currents in these cells. However, the kinetics of the ligand-gated currents differ. AMPA- and quisqualate-elicited currents rapidly desensitize, whereas kainate-gated currents do not (Fig. 7a). The desensitization at AMPA/quisqualate receptors can be reduced (Fig. 7b) by adding cyclothiazide (33), which stabilizes the receptor in an active (or non-desensitized) state (33, 34).

Each non-NMDA receptor is formed from the co-assembly of several subunits (25, 35, 36). To date, seven subunits (named GluR1 through GluR7) have been cloned (22, 35-40). Expression of subunit clones in *Xenopus* oocytes revealed that GluR5, GluR6, and GluR7 (along with subunits KA1 and KA2) co-assemble to form kainate(-preferring) receptors, whereas GluR1, GluR2, GluR3, and GluR4 are assembled into AMPA(-preferring) receptors (25).

NMDA Receptors

Glutamate binding onto an NMDA receptor also opens non-selective cation channels, resulting in a conductance increase. However, the high conductance channel associated with these receptors is more permeable to Ca^{2+} than Na^+ ions (27), and NMDA-gated currents typically have slower kinetics than kainate- and AMPA-gated channels. As the name suggests, NMDA is the selective agonist at these receptors. The compounds MK-801, AP-5 (2-amino-5-phosphonopentanoic acid), and AP-7 (2-amino-7-phosphoheptanoic acid) are NMDA receptor antagonists.

NMDA receptors are structurally complex, with separate binding sites for glutamate, glycine, magnesium ions (Mg^{2+}), zinc ions (Zn^{2+}), and a polyamine recognition site (Fig. 6b). There is also an antagonist binding site for PCP and MK-801 (41). The glutamate, glycine, and magnesium binding sites are important for receptor

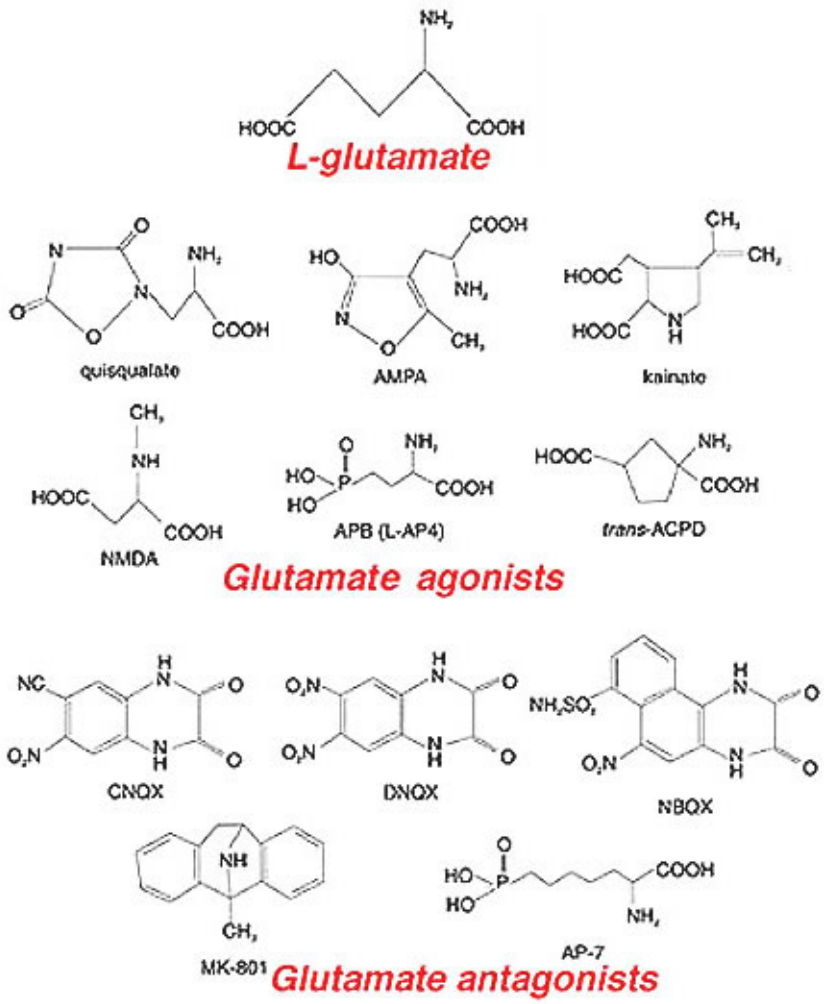

Figure 4. Glutamate receptor agonists and antagonists.

activation and gating of the ion channel. In contrast, the zinc and polyamine sites are not needed for receptor activation but affect the efficacy of the channel. Zinc blocks the channel in a voltage-independent manner (42). The polyamine site (43, 44) binds compounds such as spermine or spermidine, either potentiating (43, 44) or inhibiting (44) the activity of the receptor, depending on the combination of subunits forming each NMDA receptor (44).

To date, five subunits (NR1, NR2a, N2b, N2c, and N2d) of NMDA receptors have been cloned (45-49). As with non-NMDA receptors, NMDA receptor subunits can co-assemble as homomers (i.e., five NR1 subunits) (23, 49) or heteromers (one NR1 + four NR2 subunits) (23, 46-48). However, all functional NMDA receptors express the NR1 subunit (23, 25, 46).

The glutamate, glycine, and Mg^{2+} binding sites confer both ligand-gated and voltage-gated properties onto NMDA receptors. NMDA receptors are ligand gated because the binding of glutamate (ligand) is required to activate the channel. In addition, micromolar concentrations of glycine must also be present (Fig. 8) (50, 51). The requirement for both glutamate and glycine makes them co-agonists (51) at NMDA receptors.

Mg^{2+} ions provide a voltage-dependent block of NMDA-gated channels (52). This can be seen in the current-voltage (I-V) relationship presented in Fig. 9 (from Nowak et al. (52)). I-V curves plotted from currents recorded in the presence of Mg^{2+} have a characteristic J-shape (Fig. 9, dotted line), whereas a linear relationship is calculated in Mg^{2+}-free solutions (Fig. 9, solid line). At negative membrane potentials, Mg^{2+} ions occupy the

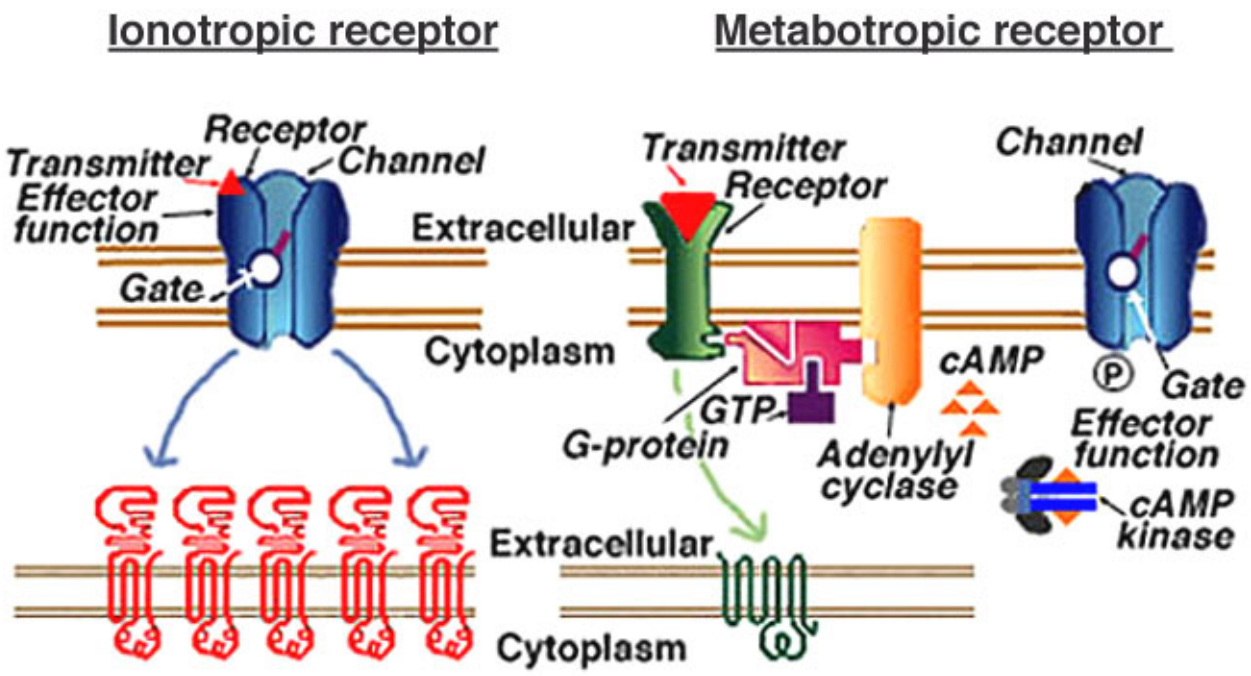

Fig. 5a. Ionotropic receptors and their associated ion channels form one complex (top). Each iGluR is formed from the co-assembly of multiple (4-5) subunits (From Kandel et al., 1991).

Fig. 5b. Metabotropic receptors are coupled to their associated ion channels by a second messenger cascade (top). Each mGluR is composed of one polypeptide, which is coupled to a G-protein (from Kandel et al., 1991).

Figure 5. Ionotropic and metabotropic glutamate receptors and channels. From Kandel et al. (127).

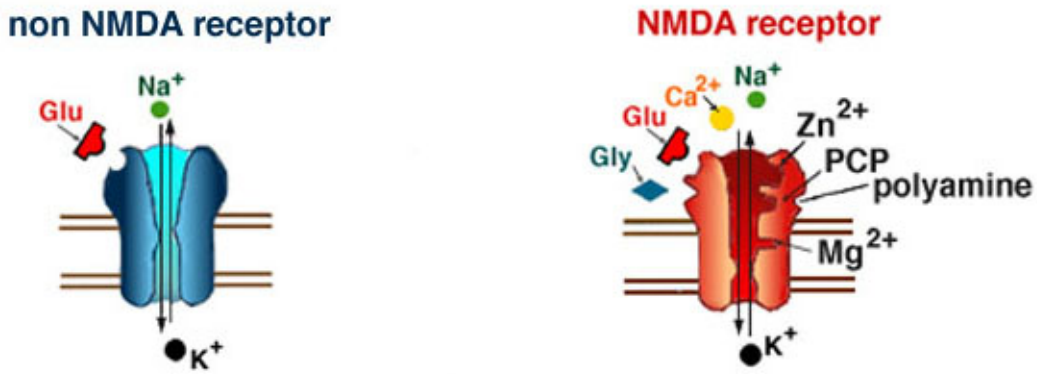

Fig. 6a. Non-NMDA receptors are selectively agonized by kainate, AMPA and quisqualate. The associated ion channels are more perm eable to Na+ and K+ ions tha Ca+2 (from Kandel et al,.1991).

Fig. 6b. NMDA receptors are structurally complex, with separate binding sites for glutamate, glycine MG+2, Zn+2 and polyamines. NMDA-gated channels are more permeable to Ca+2 than Na+ ions (from Kandel et al., 1991).

Figure 6. Comparison between NMDA and non-NMDA receptors. From Kandel et al. (127).

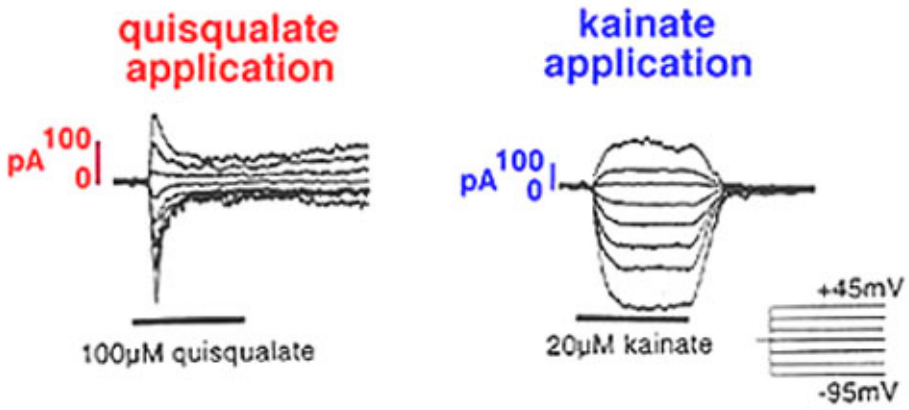

Fig. 7a. Families of whole-cell current traces show the rapid kinetics and desensitization of quisqualate- (and AMPA-) gated currents (left traces). Kainate-gated currents (right), in contrast, do not desensitize (from Gilbertson et al., 1991, Fig. 1).

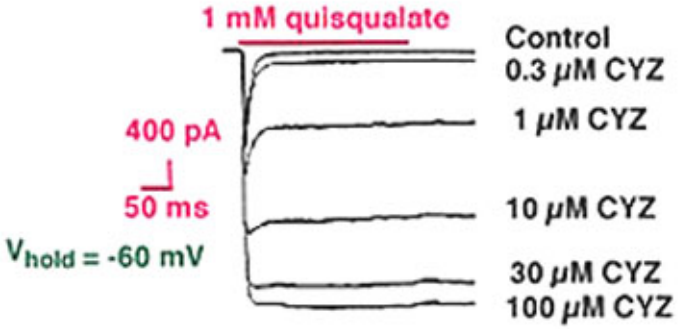

Fig. 7b. Cyclothiazide (CYZ) reduces desensitization at quisqualate receptors in a concentration-dependent manner (from Yamada and Tang, 1993, Fig. 2).

Figure 7. Whole-cell patch clamp to show quisqualate- and kainate-gated currents.

binding site, causing less current to flow through the channel. As the membrane depolarizes, the Mg^{2+} block is removed (52).

Retinal ganglion cells and some amacrine cell types express functional NMDA receptors in addition to non-NMDA receptors (i.e., 29, 53-57). The currents elicited through these different iGluR types can be distinguished pharmacologically. Non-NMDA receptor antagonists block a transient component of the ganglion cell light response, whereas NMDA receptor antagonists block a more sustained component (29, 53, 57, 58). These findings suggest that the currents elicited through colocalized NMDA and non-NMDA receptors mediate differential contributions to the ON- and OFF-light responses observed in ganglion cells (53).

Metabotropic Glutamate Receptors

Unlike ionotropic receptors, which are directly linked to an ion channel, metabotropic receptors are coupled to their associated ion channel through a second messenger pathway. Ligand (glutamate) binding activates a G-protein and initiates an intracellular cascade (59). Metabotropic glutamate receptors (mGluRs) are not co-

Figure 8. NMDA receptor activation.

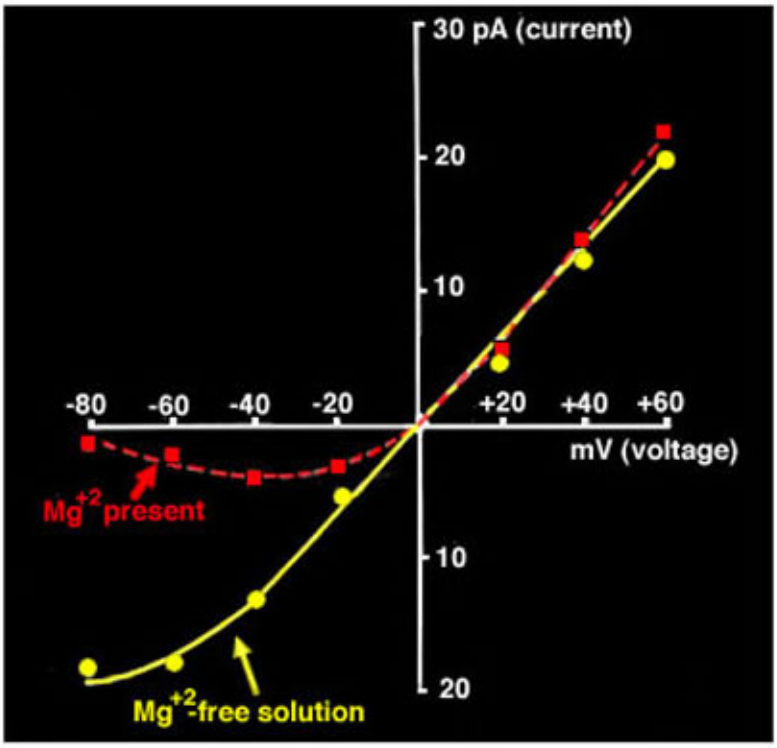

Figure 9. Mg^{2+} ions block NMDA receptor channels.

assembled from multiple subunits but are one polypeptide (Fig. 5b). To date, eight mGluRs (mGluR1 through mGluR8) have been cloned (60-66). These receptors are classified into three groups (I, II, and III) based on structural homology, agonist selectivity, and their associated second messenger cascade (Table 1) (reviewed in Nakanishi (67), Knopel et al. (68), Pin and Bockaert (69), and Pin and Duvoisin (70)).

In brief, Group I mGluRs (mGluR1 and mGluR5) are coupled to the hydrolysis of fatty acids and the release of calcium from internal stores. Quisqualate and *trans*-ACPD are Group I agonists. Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7, and mGluR8) receptors are considered inhibitory because they are coupled to the downregulation of cyclic nucleotide synthesis (70). L-CCG-1 and *trans*-ACPD agonize Group II receptors; L-AP4 (also called APB) selectively agonizes Group III receptors. *In situ* hybridization studies have revealed that the mRNAs encoding Groups I, II, and III mGluRs are present in retina (see below); however, with the exception of the APB receptor, the function of all of these receptor types in retina has not been characterized.

Table 1. **Metabotropic glutamate receptor groups (from Pin and Duvoisin (70)). .**

Group	mGluR	Agonist(s)	Intracellular pathway
I	mGluR1, mGluR5	quisqualate, ACPD	Increase phospholipase C activity, increase cAMP levels, increase protein kinase A activity
II	mGluR2, mGluR3	L-CCG-1, ACPD	Decrease cAMP levels
III	mGluR4, mGluR6. mGluR7, mGluR8	L-AP4 (APB)	Decrease cAMP or cGMP levels

APB Receptor

In contrast to non-NMDA and NMDA receptors, glutamate binding onto an APB receptor elicits a conductance decrease (71-73) because of the closure of cGMP-gated, non-selective cation channels (74) (Fig. 10).

APB application selectively blocks the ON-pathway in the retina (Fig. 11) (73), i.e., ON-bipolar cell responses and the ON-responses in amacrine cells (75) and ganglion cells (29, 76, 77) are eliminated by APB. Experimental evidence (73, 78) suggests that the APB receptor is localized to ON-bipolar cell dendrites. Inhibition of amacrine and ganglion cell light responses, therefore, is due to a decrease in the input from ON-bipolar cells, not a direct effect on postsynaptic receptors.

APB (2-amino-4-phosphobutyric acid, also called L-AP4) is the selective agonist for all Group III mGluRs (mGluR4, mGluR6, mGluR7, and mGluR8). So, which is the APB receptor located on ON-bipolar cell dendrites? MGluR4, mGluR7, and mGluR8 expression has been observed in both the inner nuclear layer and the ganglion cell layer (61, 79), suggesting that these mGluRs are associated with more than one cell type. In contrast, mGluR6 expression has been localized to the inner nuclearmlayer (INL) (64, 79) and the outer plexiform layer (OPL) (80), where bipolar cell somata and dendrites are located. Furthermore, ON-responses are abolished in mice lacking mGluR6 expression (81). These mutants also display abnormal ERG b-waves, suggesting an inhibition of the ON-retinal pathway at the level of bipolar cells (81). Taken together, these findings suggest that the APB receptor on ON-bipolar cells is mGluR6.

Glutamate Transporters and Transporter-like Receptors

Glutamate transporters have been identified on photoreceptors (15, 21, 82) and Muller cells (15, 16). From glutamate labeling studies, the average concentration of glutamate in photoreceptors, bipolar cells, and ganglion cells is 5 mM (10). Physiological studies using isolated cells indicate that only μM levels of glutamate are required to activate glutamate receptors (32, 83, 84). Thus, the amount of glutamate released into the synaptic cleft is several orders of magnitude higher than the concentration required to activate most postsynaptic receptors. High-affinity glutamate transporters located on adjacent neurons and surrounding glial cells rapidly remove glutamate from the synaptic cleft to prevent cell death (17). Five glutamate transporters, EAAT-1 (or GLAST), EAAT-2 (or GLT-1), EAAT-3 (or EAAC-1), EAAT-4, and EAAT-5, have been cloned (85-90).

Glutamate transporters are pharmacologically distinct from both iGluRs and mGluRs. L-Glutamate, L-aspartate, and D-aspartate are substrates for the transporters (21, 82, 91); glutamate receptor agonists (20, 21, 82, 91) and antagonists (82, 92) are not. Glutamate uptake can be blocked by the transporter blockers dihydrokainate (DHKA) and DL-*threo*-β-hydroxyaspartate (HA) (82, 92).

Glutamate transporters incorporate glutamate into Muller cells along with the co-transport of three Na^+ ions (91, 93) and the antiport of one K^+ ion (93, 94) and either one OH– or one HCO^{3-} ion (94) (Fig. 12). The excess sodium ions generate a net positive inward current, which drives the transporter (91, 93). More recent findings indicate that a glutamate-elicited chloride current is also associated with some transporters (85, 95).

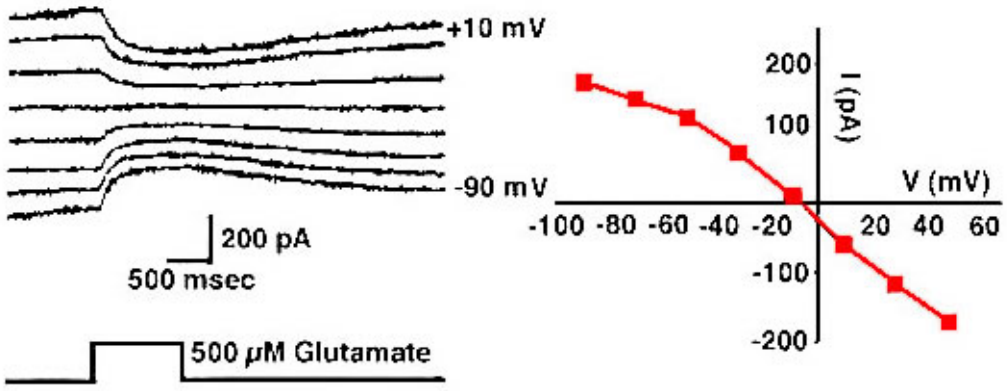

Figure 10. Whole-cell current traces to show kinetics of APB receptor-gated currents.

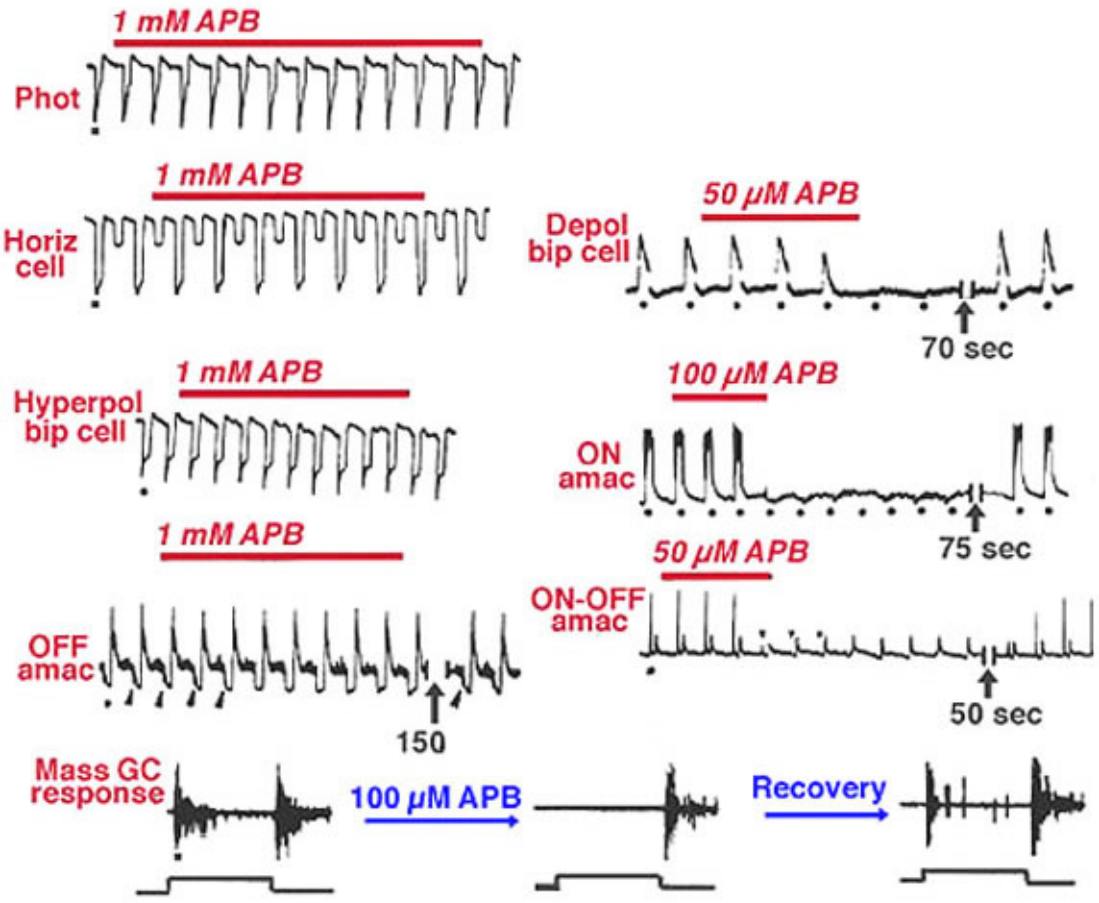

Figure 11. Intracellular recordings to show that APB selectively antagonizes the ON-pathways.

It should be noted that the glutamate transporters located in the plasma membrane of neuronal and glial cells (discussed in this section) are different from the glutamate transporters located on synaptic vesicles within presynaptic terminals (see General Overview of Synaptic Transmission). The transporters in the plasma membrane transport glutamate in a Na^+- and voltage-dependent manner independent of chloride (17, 91, 93). L-Glutamate, L-aspartate, and D-aspartate are substrates for these transporters (91). In contrast, the vesicular

transporter selectively concentrates glutamate into synaptic vesicles in a Na_+-independent, ATP-dependent manner (4-6) that requires chloride (4, 6).

Glutamate receptors with transporter-like pharmacology have been described in photoreceptors (96-98) and ON-bipolar cells (99, 100). These receptors are coupled to a chloride current. The pharmacology of these receptors is similar to that described for glutamate transporters, because the glutamate-elicited current is: 1) dependent upon external Na^+; 2) reduced by transporter blockers; and 3) insensitive to glutamate agonists and antagonists. However, altering internal Na^+ concentration does not change the reversal potential (100) or the amplitude (96, 99) of the glutamate-elicited current, suggesting that the receptor is distinct from glutamate transporters. At the photoreceptor terminals, the glutamate-elicited chloride current may regulate membrane potential and subsequent voltage-gated channel activity (99). Postsynaptically, this receptor is believed to mediate conductance changes underlying photoreceptor input to ON-cone bipolar cells (99).

Localization of Glutamate Receptor Types in the Retina

Photoreceptor, bipolar, and ganglion cells compose the vertical transduction pathway in the retina. This pathway is modulated by lateral inputs from horizontal cells in the distal retina and amacrine cells in the proximal retina (Fig. 13). As described in the previous sections, photoreceptor, bipolar, and ganglion cells show glutamate immunoreactivity. Glutamate responses have been electrically characterized in horizontal and bipolar cells, which are postsynaptic to photoreceptors, and in amacrine and ganglion cells, which are postsynaptic to bipolar cells. Taken together, these results suggest that glutamate is the neurotransmitter released by neurons in the vertical pathway. Recent *in situ* hybridization and immunocytochemical studies have localized the expression of iGluR subunits, mGluRs, and glutamate transporter proteins in the retina. These findings are summarized below.

Retinal Neurons Expressing Ionotropic Glutamate Receptors

In both higher and lower vertebrates, electrophysiological recording techniques have identified ionotropic glutamate receptors on the neurons composing the OFF-pathway (Table 2). In the distal retina, OFF-bipolar cells (Fig. 14) (84, 101, 102) and horizontal cells (Fig. 15) (32, 103, 104) respond to kainate, AMPA, and quisqualate application, but not NMDA nor APB. (However, NMDA receptors have been identified on catfish horizontal cells (105, 106), and APB-induced hyperpolarizations have been reported in some fish horizontal cells (107-109)).

Non-NMDA agonists also stimulate both amacrine cells (Fig. 16a) (28, 54, 55) and ganglion cells (Fig. 16b) (29, 31, 53, 57, 58). Ganglion cells responses to NMDA have been observed (29, 53, 55-57), whereas NMDA responses have been recorded in only some types of amacrine cells (28, 54, 55) but see Hartveit and Veruki (110).

Consistent with this physiological data, antibodies to the different non-NMDA receptor subunits differentially label all retinal layers (Table 3) (111-114), and mRNAs encoding the different non-NMDA iGluR subunits are similarly expressed (115-117). In contrast, mRNAs encoding NMDA subunits are expressed predominantly in the proximal retina, where amacrine and ganglion cells are located (INL, IPL, GCL) (Table 3) (111, 115), although mRNA encoding the NR2a subunit (111) has been observed in the OPL and antibodies to the NR2d (118) and the NR1 subunits (112) label rod bipolar cells.

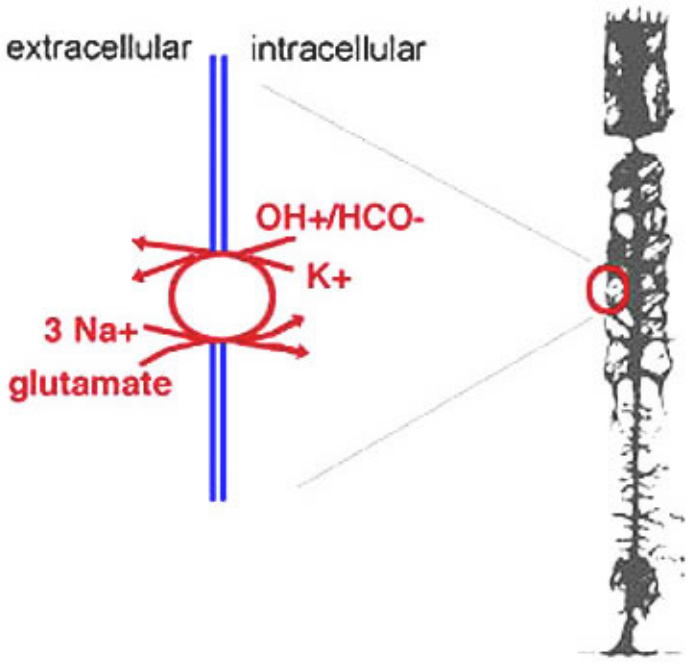

Figure 12. Glutamate transporters in Muller cells are electrogenic.

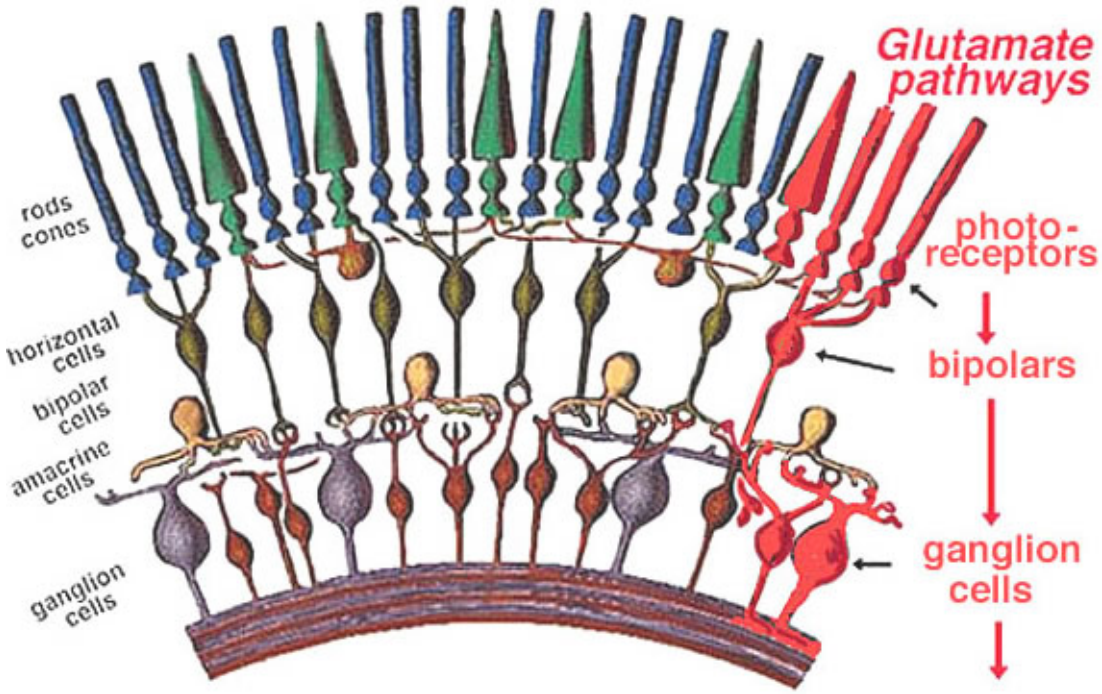

Figure 13. The types of neurons in the vertebrate retina.

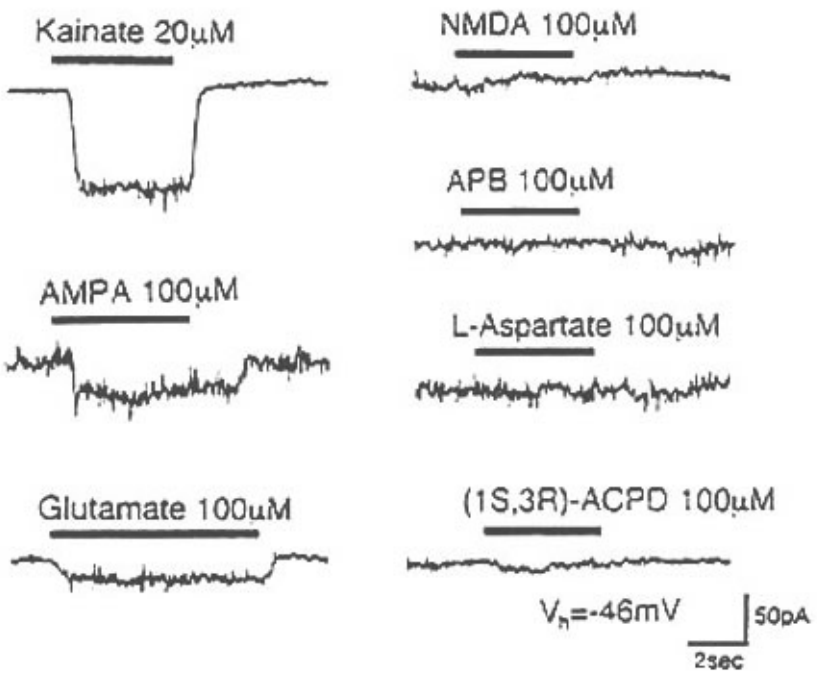

Figure 14. Whole-cell currents in OFF bipolar cells.

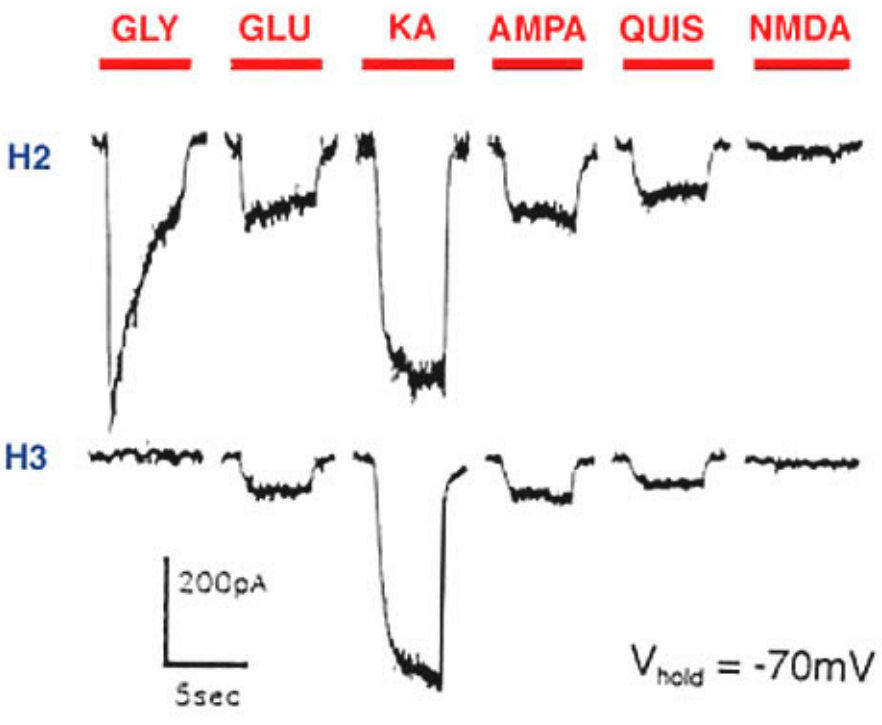

Figure 15. Whole-cell currents in horizontal cells.

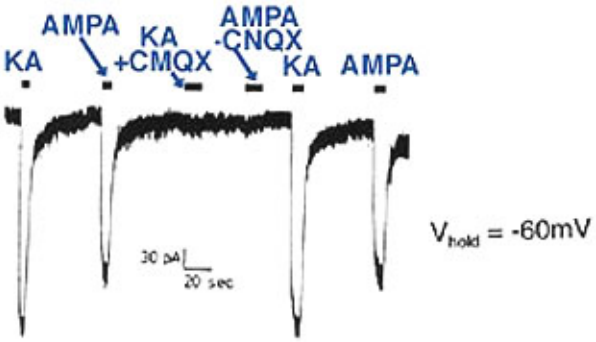

Fig. 16a. Representative whole cell current trace showing the glutamate receptors on amacrine cells are depolarized by the iGluR agonists kainate and AMPA. These responses are blocked by the antagonist CNQX (from Boos et al., 1993, Fig. 13.).

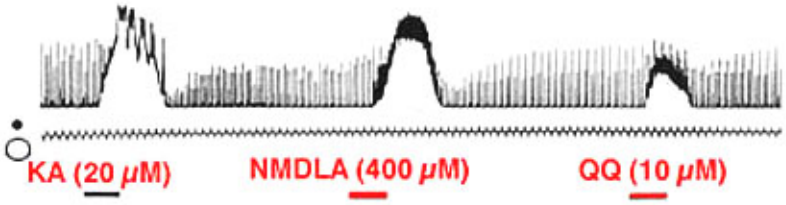

Fig. 16b. Representative ratemeter recording showing an increase in firing rate in ganglion cells in response to NMDA, kainate and quisqualate application (from Massey and Miller, 1988, Fig. 10)

Figure 16. Glutamate receptors on amacrine and ganglion cells.

Table 2. Glutamate receptor types on retinal neurons, electrophysiological measurements.

Retinal cell type	Non-NMDA receptor	NMDA receptor	mGluR	Glutamate receptor with transporter-like pharmacology	Species	Reference
Photoreceptors				++ (cones)	Salamander	Eliasof & Werblin (82); Picaud et al (98).
				++ (rods)	Salamander	Grant & Werblin (96)
OFF-bipolar cells	++				Mudpuppy	Slaughter & Miller (73, 128)
	++				Cat	Sasaki & Kaneko (84)
	++				Salamander	Hensley et al. (58)
	++				Rat	Euler et al. (102)
	++				Mudpuppy	Slaughter & Miller (128)
ON-bipolar cells	++		++ (APB)		Mudpuppy	Slaughter & Miller (73, 128)
			++ (APB)	++	White perch	Grant & Dowling (99, 100)

Table 2 continued from previous page.

Retinal cell type	Non-NMDA receptor	NMDA receptor	mGluR	Glutamate receptor with transporter-like pharmacology	Species	Reference
			++ (APB)		Salamander	Hirano & MacLeish (129)
			++ (L-AP4)		Salamander	Hensley et al. (58)
			++ (AP-4)		Rat	Euler et al. (101)
			++ (APB and cGMP)		Salamander	Nawy & Jahr (74)
			++ (APB and cGMP)		Cat	de la Villa et al. (130)
Horizontal cells	++				White perch	Zhou et al. (32)
	++				Mudpuppy	Slaughter & Miller (128)
	++				Salamander	Yang & Wu (104)
	++	++			Catfish	O'Dell & Christensen (106); Eliasof & Jahr (105)
Amacrine cells	++ (AII)				Rat	Boos et al. (28)
	++	++			Mudpuppy	Slaughter & Miller (128)
	++	++			Rabbit	Massey & Miller (55)
	++	++			Rat	Harveit & Veruki (110)
	++ (transient & sustained AC)	++ (transient AC)			Salamander	Dixon & Copenhagen (54)
Ganglion cells	++	++			Salamander	Diamond & Copenhagen (53); Mittman et al (57); Hensley et al (58).
	++	++			Primates	Cohen & Miller (29)
	++	++			Rat	Aizenman et al. (83)
	++	++			Mudpuppy	Slaughter & Miller (128)
	++	++			Cat	Cohen & Miller (29)
	++	++			Rabbit	Massey & Miller (55, 56)

Table 3. Ionotropic glutamate receptor expression in retinal neurons and retinal layers, immunocytochemistry, and *in situ* hybridization.

Retinal cell type or layer	Non-NMDA receptor subunits	NMDA receptor subunits	Species	Reference
Photoreceptors	GluR6/7 (single cone outer segments)		Goldfish	Peng et al. (113)
	GluR1 (cone pedicles)		Cat	Pourcho et al. (114)
OPL	GluR2, GluR2/3, GluR6/7		Rat	Peng et al. (113)
		NR2A (punctate)	Cat	Harveit et al. (111)

Table 3 continued from previous page.

Retinal cell type or layer	Non-NMDA receptor subunits	NMDA receptor subunits	Species	Reference
	GluR2, GluR2/3 (photoreceptors)		Goldfish	Peng et al. (113)
Bipolar cells	GluR2 (Mb cells)		Goldfish	Peng et al. (113)
	GluR2, GluR2/3		Rat	Peng et al. (113)
		NR2D (RBC)	Rat	Wenzel et al. (118)
	GluR2 and/or GluR4	NR1 (RBC)	Rat	Hughes (112)
	GluR2 (RBC)		Rat	Hughes et al. (117)
Horizontal cells	GluR6/7		Goldfish	Peng et al. (113)
	GluR2/3		Cat	Pourcho et al. (114)
INL	GluR2/3, GluR6/7		Rat	Peng et al. (113)
		NR2A (inner)	Rat	Hartveit et al. (111)
	GluR1, 2, 5 > GluR4 (outer third), GluR1, 2, 5 (middle third), GluR1-5 (inner third)		Rat	Hughes et al. (117)
	GluR1-7		Rat, cat	Hamassaki-Britto et al. (116)
	KA2 (homogeneous), GluR6 (inner), GluR7 (inner two-thirds)	NR1 (homogeneous), NR2A-B (inner third, patchy), NR2C (inner two-thirds)	Rat	Brandstatter et al. (115)
IPL	GluR1, GluR2/3, GluR6/7		Rat	Peng et al. (113)
		NR2A	Rat, cat, rabbit, monkey	Harveit et al. (111)
Amacrine cells	GluR6	NR2A-C	Rat	Brandstatter et al. (115)
	GluR2/3		Cat	Pourcho et al. (114)
	GluR1, GluR2/3		Rat	Peng et al. (113)
Ganglion cells	GluR1		Rat	Peng et al. (113)
GCL	GluR2/3, GluR6/7		Rat	Peng et al. (113)
	GluR1-5		Rat	Hughes et al. (117)
	GluR1-7		Rat, cat	Hamassaki-Britto et al. (115)
	GluR6/7, KA2	NR1, NR2A-C	Rat	Brandstatter et al. (115)
Muller cells	GluR4		Rat	Peng et al. (113)

Retinal Neurons Expressing Metabotropic Glutamate Receptors

All metabotropic glutamate receptors, except mGluR3, have been identified in retina either through antibody staining (113, 114, 119, 120) or *in situ* hybridization (61, 64, 79). MGluRs are differentially expressed throughout the retina, specifically in the outer plexiform layer, inner nuclear layer, inner plexiform layer, and the ganglion cell layer (Table 4). Although different patterns of mGluR expression have been observed in the retina, only the APB receptor on ON-bipolar cells has been physiologically examined.

Table 4. Metabotropic glutamate receptor expression in retinal neurons and retinal layers, immunocytochemistry, and in situ hybridization.

Retinal cell type or layer	Group I	Group II	Group III	Species	Reference
OPL	mGluR1alpha, mGluR5a (RBC dendrites)			Rat	Koulen et al. (120)
			mGluR6 (RBC dendrites)	Rat	Nomura et al. (80)
INL	mGluR8			Mouse	Duvoisin et al. (61)
			mGluR6	Rat	Nakajima et al. (64)
	mGluR5 (BC, HC), mGluR1 (AC)	mGluR2 (AC)	mGluR6 (RBC), mGluR7 (BC), mGluR4, 7 (AC)	Rat	Hartveit et al. (79)
IPL	mGluR1alpha			Rat	Peng et al. (113)
			mGluR7 (CBC terminals; AC dendrites; few GC dendrites)	Rat	Brandstatter et al. (115)
	mGluR1alpha, mGluR5a (AC dendrites)			Rat	Koulen et al. (120)
Amacrine cells	mGluR1alpha			Rat	Peng et al. (113)
	mGluR1alpha			Cat	Pourcho et al. (114)
Ganglion cells	mGluR1alpha			Rat	Peng et al. (113)
GCL			mGluR8	Mouse	Duvoisin et al. (61)
	mGluR1alpha	mGluR2/3		Cat	Pourcho et al. (114)
	mGluR1	mGluR2	mGluR4, 7	Rat	Hartveit et al. (79)

Retinal Neurons Expressing Glutamate Transporters

The glutamate transporters GLAST, EAAC1, and GLT-1have been identified in retina (Table 5). GLAST (L-**gl**utamate/L-**as**partate **t**ransporter) immunoreactivity is found in all retinal layers (121) but not in neuronal tissue. GLAST is localized to Muller cell membranes (121-124). In contrast, EAAC-1 (**e**xcitatory **a**mino **a**cid **c**arrier-1) antibodies do not label Muller cells or photoreceptors. EAAC-1 immunoreactivity is observed in ganglion and amacrine cells in chicken, rat, goldfish, and turtle retinas. In addition, bipolar cells positively labeled with EAAC-1 antibody in lower vertebrates, and immunopositive horizontal cells were observed in rat (90). GLT-1 (**gl**utamate **t**ransporter-1) proteins have been identified in monkey (125), rat (124), and rabbit (126) bipolar cells. In addition, a few amacrine cells were weakly labeled with the GLT-1 antibody in rat (124), as were photoreceptor terminals in rabbit (126).

Table 5. Glutamate transporters in retinal neurons and retinal layers, immunocytochemical localizations.

Retinal cell type	EAAC-1	GLAST	GLT-1	Species	Reference
Photoreceptors			+ (cone soma to pedicles)	Rabbit	Massey et al. (126)
OPL	++			Rat	Rauen et al. (124)
			++ (rod spherules > cone pedicles)	Rabbit	Massey et al. (126)
Horizontal cells	++			Rat	Schultz & Stell (90); Rauen et al (124).

Table 5 continued from previous page.

Retinal cell type	EAAC-1	GLAST	GLT-1	Species	Reference
Bipolar cells			++ (2 types of CBCs)	Rabbit	Massey et al. (126)
	++ (faint)		++	Rat	Rauen et al. (124)
	++			Turtle, salamander	Schultz & Stell (90)
			++ (DB2, flat midget bipolar cells)	Monkey	Grunert et al. (125)
IPL			++ (diffuse)	Rabbit	Massey et al. (126)
	++		++	Rat	Rauen et al. (124)
	++			Goldfish, salamander, turtle, chicken, rat	Schultz & Stell (90)
Amacrine cells	++		++	Rat	Rauen et al. (124)
	++				Schultz & Stell (90)
Ganglion cells	++			Chicken, rat, goldfish, turtle	Schultz & Stell (90)
	++			Rat	Rauen et al. (124)
Muller cells		++		Rat	Rauen et al. (124); Lehre et al (123); Deroiche & Rauen (122)

Summary and Conclusions

Histological analyses of presynaptic neurons and physiological recordings from postsynaptic cells suggest that photoreceptor, bipolar, and ganglion cells release glutamate as their neurotransmitter. Multiple glutamate receptor types are present in the retina. These receptors are pharmacologically distinct and differentially distributed. IGluRs directly gate ion channels and mediate rapid synaptic transmission through either kainate/AMPA or NMDA receptors. Glutamate binding onto iGluRs opens cation channels, depolarizing the postsynaptic cell membrane. Neurons within the OFF-pathway (horizontal cells, OFF-bipolar cells, amacrine cells, and ganglion cells) express functional iGluRs. mGluRs are coupled to G-proteins. Glutamate binding onto mGluRs can have a variety of effects, depending on the second messenger cascade to which the receptor is coupled. The APB receptor, found on ON-bipolar cell dendrites, is coupled to the synthesis of cGMP. At these receptors, glutamate decreases cGMP formation, leading to the closure of ion channels. Glutamate transporters, found on glial and photoreceptor cells, are also present at glutamatergic synapses (Fig. 17). Transporters remove excess glutamate from the synaptic cleft to prevent neurotoxicity. Thus, postsynaptic responses to glutamate are determined by the distribution of receptors and transporters at glutamatergic synapses which, in retina, determine the conductance mechanisms underlying visual information processing within the ON- and OFF-pathways.

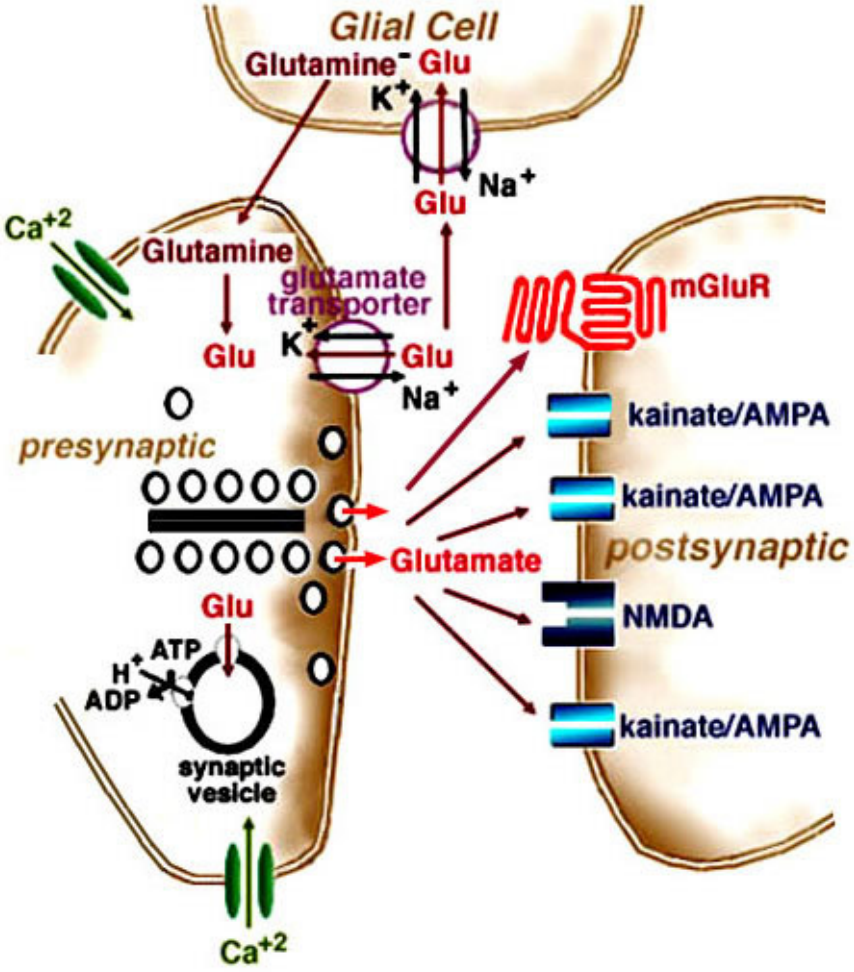

Figure 17. The ribbon glutamatergic synapse in the retina.

About the Author

Dr. Victoria Connaughton was born in Sellersville, Pennsylvania. She received her B.A. from Bucknell University in Biology in 1989 and her Ph.D. in Marine Studies from The University of Delaware in 1994. She is currently an Assistant Professor in the Biology Department at American University, Washington, DC. In her thesis work under Dr. Charles Epifano, she studied the visually guided feeding behavior of larval fish. Dr. Connaughton pursued postdoctoral studies with Dr. Greg Maguire at the University of Houston and Dr. Ralph Nelson at the National Institutes of Health. Dr. Connaughton's current research interests include electrophysiological examination of zebrafish mutants with visual system defects and the characterization of light responses in zebrafish retinal bipolar cells.

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