Synaptic Organization and Ionic Basis of On and Off Channels in Mudpuppy Retina

III. *A Model of Ganglion Cell Receptive Field Organization Based on Chloride-Free Experiments*

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ABSTRACT A chloride-free environment produces selective changes in the retinal network which include a separation of *on* and *off* channels. The identification of chloride-sensitive and insensitive neuronal activity permits identification of some of the connections and intervening polarities of synaptic interactions which are expressed in ganglion cell receptive field organization. These experiments support previous suggestions that surround antagonism is dependent on horizontal cell activity. In addition they suggest a model of the neuronal connections which subserve *on-center, off-center,* and *on-off* ganglion cells. Experimental tests of the on-off ganglion cell model favor the idea that this type of ganglion cell receives inhibitory input from amacrine cells and excitatory activation from depolarizing and hyperpolarizing bipolar cells.

In recent years intracellular recording experiments in the vertebrate retina have provided considerable insight into the cellular mechanisms and pathways which underlie ganglion cell receptive field organization. These experiments indicate that receptors hyperpolarize to light stimulation (Bortoff, 1964; Tomita, 1965; Werblin and Dowling, 1969; Toyoda et al., 1969; Kaneko, 1970; Baylor et al., 1971; Brown and Pinto, 1974). Two types of bipolar cells have been demonstrated. One type hyperpolarizes and a second type depolarizes in response to a centrally located light stimulus; stimulation of the surrounding region produces polarity changes which are opposite to those of center stimulation. Thus the bipolar cells are anatagonistically organized and the separation of "on" and "off" channels occurs at the level of receptor-bipolar cell interaction. It is reasonable to assume that on ganglion cells are subserved by one type of bipolar, and off by the other.

The next level of inquiry is to ask which bipolar cell type is connected to the on ganglion cell and which to the off ganglion cell. Intracellular recording experiments show that on ganglion cells are depolarized during light stimulation and

off ganglion cells are hyperpolarized (Wiesel, 1959; Werblin and Dowling, 1969; Dacheux et al., 1973). The depolarizing bipolar could be excitatory to the on cells or inhibitory to the off cells. By the same reasoning, the hyperpolarizing bipolar could activate the on cells by a disinhibitory mechanism, or the off cells by a disfacilitatory influence. This argument assumes that transmitter release mechanisms in the retina are in harmony with those established at other synapses and that depolarization is a prerequisite for transmitter release. Studies of turtle (Trifonov and Byzov, 1965; Cervetto and Piccolino, 1974), skate (Dowling and Ripps, 1973), and mudpuppy (Dacheux and Miller, 1976) suggest that receptors release a transmitter in the depolarized dark state and that the light-evoked hyperpolarization reduces the rate of transmitter release. At least at the receptor level, transmitter release mechanisms appear to be similar to those described in other parts of the nervous system.

One method of approaching the problem of bipolar connections and intervening polarities would be to obtain simultaneous intracellular recordings from the pre- and postsynaptic cells and evaluate the postsynaptic changes induced by current injection into the presynaptic neuron. Experiments of this type are technically difficult and have been successfully applied in only a few instances (Katz and Miledi, 1966; Hagiwara and Tasaki, 1958; Takeuchi and Takeuchi, 1962). Several workers (Maksimova, 1970; Naka and Nye, 1971; Naka and Witkovsky, 1972; Schwartz, 1972) have recorded simultaneously from horizontal cells (intracellularly) and ganglion cells (extracellularly) which are functionally interconnected. While these observations have not identified the type of bipolar cell-ganglion cell interaction, they have provided significant insights into the functional role of horizontal cells and the general technique holds promise for the identification problem considered here. An alternative approach would be to apply a method which selectively interrupted one of the on or off mechanisms and to evaluate by intracellular recording techniques the remaining pathway, thereby revealing the type of bipolar cell which is connected to a particular class of ganglion cells. Several restrictions imposed on this method would be: *(a)* Receptors must remain functional in order to activate the remaining retinal network. *(b)* One of the two types of bipolar cells must be abolished. *(c)* The ganglion cell activity associated with the remaining bipolar should remain responsive to light stimulation. In this way the "unaffected channel" will have a receptor-activated-bipolar cell-mediated-ganglion cell discharge.

In previous studies we have evaluated the highly selective changes in the retinal network which follow the removal of external chloride ions in the perfused retina eyecup of rabbit and mudpuppy (Miller and Dacheux, 1973; 1975 *a*, 1976 *a*, *b*). This analysis demonstrates that a chloride-free (c-f) environment reduces the functional connection between receptors and cells of the inner retina to the hyperpolarizing bipolars (HPB). Light-evoked activity of the depolarizing bipolar cells (DPB) and horizontal cells (HC) is abolished (for a summary, see Fig. 6, Miller and Dacheux, 1976 *a*). Since off-ganglion cell activity also persists in a c-f medium, it is apparent that the "dissecting nature" of this procedure results in a simplified network in which on and off channels are separated; therefore a c-f environment conforms to the above-mentioned re-

strictions. In addition, the absence of external chloride abolishes the surround antagonism of the HPB leaving the cell with only a center-type hyperpolarizing response. The loss of light-evoked activity of the HC in a c-f medium supports suggestions of other workers (Werblin and Dowling, 1969; Kaneko, 1970) that the antagonistic surround of bipolar cells is dependent on HC activity.

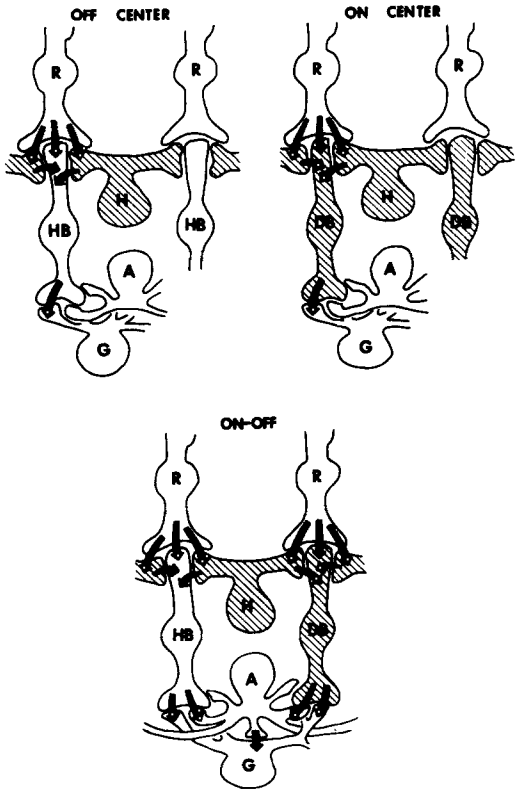

FIGURE 1. A model of receptive field organization and synaptic polarities for on-center, off-center, and on-off ganglion cells. Chloride-sensitive cells are shaded and include depolarizing bipolars and horizontal cells. The synaptic polarities indicate the action of the cell when it is in a relatively depolarized state. Cells which release a transmitter in the dark include receptors, horizontal cells, and hyperpolarizing bipolar cells. Cells which release a transmitter in response to light stimulation include the depolarizing bipolars and on-off amacrine cells.

Fig. 1 presents a model of the retinal connections underlying the three types of ganglion cells which have been considered throughout our studies (on-center, off-center, and on-off). The cells whose light-evoked responses are abolished in a c-f (DPB and HC) environment are shaded. The polarity of each connection is based on the assumption that *(a)* it is a site dependent on chemical transmission and *(b)* neurons release a transmitter at maximal rate when they are in a relatively depolarized state, and *(c)* hyperpolarization leads to a reduction in the rate of transmitter release. Thus the cells which release a transmitter in the dark

include receptors, HC's, and HPB's. The DPB's and amacrine cells (on-off type) release a transmitter during light stimulation. The evidence favoring this interpretation is discussed below.

Outer Plexiform Layer

Two important features of retinal organization are established by synaptic interactions in the outer plexiform layer: first, the separation of on and off channels takes place at the receptor-bipolar cell level, and second, the antagonistic surround mechanism appears to be established as a result of horizontal cell activity (Werblin and Dowling, 1969; Kaneko, 1970). The use of externally applied divalent cations to block synaptic transmission has contributed to our understanding of the polarities of transmission between receptors and those neurons which receive direct synaptic input from receptors. The application of these agents results in a hyperpolarization and a loss of light-evoked activity of the HC (Dowling and Ripps, 1973; Cervetto and Piccolino, 1974; Dacheux and Miller, 1976) and the HPB (Dacheux and Miller, 1976). The DPB is depolarized by externally applied cobalt (Dacheux and Miller, 1976). These observations suggest that receptors release a transmitter in the dark (Trifonov, 1968; Trifonov and Byzov, 1965) which maintains HC's and HPB's in a depolarized state, but results in a relative hyperpolarization of DPB's. These polarities are indicated in Fig. 1. Murakami et al. (1975) have shown that the application of agents such as glutamate and aspartate have opposite effects on HPB and DPB, raising the possibility that the mechanism underlying the separation of on and off channels is dependent on specializations within the bipolar cells rather than different transmitters released by receptors.

CENTER-SURROUND ORGANIZATION Intracellular recording experiments suggest that HC's mediate the surround antagonism of bipolar cells (Werblin and Dowling, 1969; Kaneko, 1970). Observations presented in the first paper of this series are consistent with this interpretation. In a c-f environment the HPB remains responsive to light, but the depolarizing surround mechanism is abolished (Miller and Dacheux, 1976 *a*). Since the light-evoked activity of HC's is also chloride dependent this observation is consistent with the identification of the HC's as the interneuron for surround antagonism. The pathway for horizontal cell action occurs either as a feedback onto receptors (Baylor et al., 1971), or as a feedforward onto bipolar cells (Werblin, 1974) or both. It is still not clear however, whether amacrine cells also contribute to center-surround organization.

What is the polarity of HC action? In Fig. 1 we have drawn the horizontal connection to the bipolar cells, since electron microscopy (Dowling and Werblin, 1969) suggests that such chemical synapses are numerous in the mudpuppy and physiological experiments indicate that a feedback influence on receptors is not well developed (Werblin, 1974). In considering the polarity of HC action a critical issue concerns the mechanism of transmitter release from HC's. Although the issue is not clearly resolved, there is evidence to support the idea that the HC's, like the receptors, release a transmitter in the depolarized dark state. Several workers have utilized the technique of simultaneous intracellular record-

ings from HC's and extracellular recordings from ganglion cells whose impulse activity is affected by intracellular current injection in the HC's (Maksimova, 1970; Naka and Nye, 1971; Naka and Witkovsky, 1972; Schwartz, 1972). These studies show that both depolarizing and hyperpolarizing current injection in the HC results in ganglion cell discharge. It is difficult to see how this could occur unless horizontal cells are releasing a transmitter in the unstimulated (dark) state and that depolarization increases, and hyperpolarization decreases the rate of transmitter release. Furthermore the influence of horizontal cell current injection on ganglion cell discharge varies according to the type of ganglion cell. Depolarization results in the type of discharge associated with center light stimulation while hyperpolarization produces the type of discharge associated with surround stimulation. Our studies of c-f effects have identified the type of bipolar cell connected to the on and off ganglion cells (see below). This identification permits on evaluation of the above experiments which are otherwise limited in providing evidence about the polarity of HC interaction. Since DPB's are connected to on cells, this means that depolarization of HC's depolarizes DPB's, but hyperpolarizes HPB's. The HC influence on bipolar cells is opposite to that of receptors. Thus in the dark DPB's are hyperpolarized by receptors and depolarized by HC's. These opposing influences would have a stabilizing effect on the membrane potential of bipolar cells. Light stimulation which activated both center and surround pathways (diffuse light stimulus) would lead to an initial reduction in transmitter release by the receptors and an initial depolarization in the DPB's, followed by a reduced rate of transmitter release from the HC's (as a result of their hyperpolarization) which would lead to a relative hyperpolarization. From this, it follows that the equilibrium potential for HC action must be somewhat more negative than the equilibrium potential of the receptor-dependent depolarizing response. In the case of the HPB, the influences of receptors and horizontal cells would be opposite to those on the DPB. In this case the HPB is depolarized by receptors, but hyperpolarized by HC's. Thus the polarities for HC action in Fig. 1 are based on the hypothesis that horizontal cells release a transmitter in the dark and it is the polarity of the dark-dependent action which is indicated.

Inner Plexiform Layer

Synaptic interactions in the outer retina establish the separation of on and off channels as well as center-surround organization (or at least a significant component of it) within the bipolars. These channels then are presented to the inner retina and the question of interest is how are these channels incorporated into ganglion cells and which bipolar cells subserve which type of ganglion cells? The evidence from c-f studies suggests that ganglion cells receive input from either one of the two bipolar cells (on-center or off-center) or from both bipolars (on-off ganglion cells).

OFF-CENTER CELLS Off-center ganglion cell activity persists in a c-f environment, although surround (on) excitation is abolished. Since the hyperpolarizing bipolar remains as the only pathway from receptor to ganglion cells under these conditions, a connection between the two cells is established. The loss of

the antagonistic surround organization of the HPB in a c-f environment (Miller and Dacheux, 1976 *a*) is sufficient to explain the absence of surround excitation in the off-center ganglion cells; it is also sufficient to attribute the loss of the surround mechanism to the loss of light-evoked activity in the horizontal cell.

What is the interconnecting polarity between HPB's and of ganglion cells? In a previous paper (Miller and Dacheux, 1976 *b*) we showed that the light-evoked hyperpolarization of off cells was not chloride dependent, and presented arguments favoring the view that it resulted from a light-evoked decrease of a dark-mediated EPSP (i.e., disfacilitation). It would seem, therefore, that the HPB releases an excitatory transmitter in the dark and that the light-evoked hyperpolarization results in a reduced level of transmitter release. This idea is consistent with suggestions of other workers that receptors release a transmitter in the dark (Trifonov and Byzov, 1965; Trifonov, 1968; Dowling and Ripps, 1973; Dacheux and Miller, 1976) and helps to explain the observation that in the dark-adapted cat, off-center cells have a higher level of spontaneous activity than on-center cells (Jung, 1964; Barlow and Levick, 1969).

ON-CENTER CELLS On ganglion cells are silent in a c-f environment; since the DPB is insensitive to light stimulation under these conditions it is inescapable that they are interconnected. Furthermore the connection must be an excitatory one since depolarization of the bipolar leads to depolarization and impulse activity in the ganglion cell.

ON-OFF GANGLION CELLS The on discharge of on-off ganglion cells is abolished in a c-f medium, but the off discharge is chloride insensitive. The loss of the on discharge can be attributed to a loss of the DPB and the persistent off discharge demonstrates a connection with the HPB. This model explains the similar latency for on and off discharges, since an identical number of neurons exist for the on and off excitatory pathways. This is in contrast to the latency pattern observed in on- and off-center cells. In the latter cells, surround excitation is always of longer latency than center excitation (Barlow et al., 1964) consistent with the view that the surround pathway involves an additional neuron (HC) compared to the center pathway (Werblin and Dowling, 1969; Kaneko, 1970). It is also apparent that the HC's do not play a significant role in the off discharge of the on-off ganglion cells.

It is characteristic of on-off cells to have an inhibitory surround (Barlow, 1953; Miles, 1972; Schwartz, 1972); light falling on a region surrounding that which gives on and off responses inhibits the excitatory on-off regions, but does not itself produce ganglion cell discharge. This pathway can be explained by having an amacrine-cell-mediated inhibitory field which is larger than the excitatory on-off field as was shown in the previous study (Miller and Dacheux, 1976 *b*).

ON-OFF AMACRINE CELLS The amacrine cells, like the on-off ganglion cells, appear to receive excitatory input from each of the two bipolar cells. In a c-f environment the on component of amacrine cells is abolished but the off component remains. In some cells a c-f medium unmasked a light-evoked hyperpolarizing response which preceded the off depolarization (see Fig. 6, Miller and Dacheux, 1976 *a*). Thus the onset of a light stimulus produces an

excitatory input from the DPB and a disfacilitatory influence from the HPB. At light off, the amacrine receives an excitatory input from the HPB and a disfacilitatory input from the DPB, thereby contributing to the transient waveform of these responses. Presumably the arrangement is such that the excitatory influences at light on and off are more influential than the disfacilitatory ones. A similar arrangement for on-off amacrine cells has been suggested by Werblin (1972) and Toyoda et al. (1973). Also the role of the amacrine cell feedback synapses onto the bipolar cell terminal may contribute to the transient nature of these responses but this is not established.

AN EXPERIMENTAL TEST OF THE ON-OFF GANGLION CELL MODEL The model of the on-off ganglion cell connections in Fig. 1 is in contrast to the suggestions of Werblin and Dowling (1969). Based on similar response patterns and anatomical observations (Dowling, 1968) these workers suggested that amacrine cells were excitatory to on-off ganglion cells. Our previous studies (Miller and Dacheux, 1976 *b*) and those of Werblin and Copenhagen (1974) suggest that amacrine cells are inhibitory to on-off ganglion cells and that this inhibition is due to a chloride-dependent IPSP.

We have further tested the on-off ganglion cell model of Fig. 1 in the following way. In a freshly excised mudpuppy eyecup, extracellular recordings were obtained from on-off ganglion cells. Intracellular amacrine cell responses were simultaneously recorded within 100 to 500 μm of the ganglion cell recording; five such simultaneous recordings were obtained. In no case did depolarizing current injection in the amacrine cell result in excitation of the on-off ganglion cell. According to the model of Fig. 1, on-off ganglion cells and amacrine cells should receive excitatory input at about the same time.

Fig. 2 *a* illustrates simultaneous amacrine and on-off ganglion cell recordings evoked by diffuse illumination. On and off impulse activity and amacrine cell responses have similar latencies. Fig. 2 *b* recorded at a fast sweep speed shows that the first ganglion cell impulse occurs between 1.8–2.2 ms after the onset of slow rising EPS response (arrow) of the amacrine cell. Since ganglion cell activity is also preceded by an EPSP, the delay between the two responses is actually less than this value. Furthermore, it is clear that the peak of the EPS response of the amacrine cell occurs after the cessation of impulse activity in the ganglion cell. If the amacrine cell were excitatory to the ganglion cell one would expect on-off ganglion cell impulse activity to "follow" the amacrine cell response with a more prolonged period of impulse activity. On the other hand the peak of the amacrine cell response does occur during the period of ganglion cell inhibition which follows on and off impulse activity (Miller and Dacheux, 1976 *b*).

Simultaneous recording experiments have on six occasions resulted in intracellular and extracellular recordings from nearby on-off ganglion cells. The advantage of this recording situation is that the IPS response, in the absence of impulse activity, can be compared to the ganglion cell impulse activity. Also, simultaneous recordings ensure that the responses are obtained under equivalent conditions and state of adaptation. The upper trace in Fig. 2 *c* shows an intracellularly recorded IPSP, inverted to a depolarizing response by current injection. The lower trace shows the extracellular recording of an on-off gan-

glion cell. The onset of the light stimulus is indicated by the dark bar. The intracellular recording consists of an initial slow rising response EPSP followed by a faster rising inverted IPSP. It is clear that the onset of ganglion cell discharge and the intracellularly recorded slow potential occur at about the same

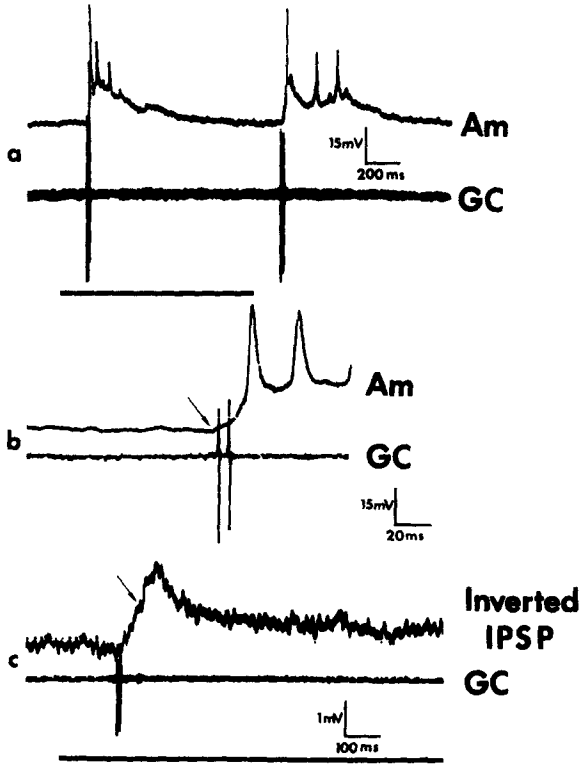

FIGURE 2. *(a)* Simultaneous intracellular amacrine cell recording and extracellular ganglion cell recording. Cells within 500 μm of each other. Diffuse light stimulus (duration indicated by dark bar) evokes ganglion cell activity and amacrine cell responses of nearly equal latency (voltage calibration applies to amacrine cell recording: extracellular ganglion cell recordings uncalibrated). *(b)* Amacrine and ganglion cell recording displayed at fast time base. Onset of slow rising EPSP in amacrine cell (arrow) precedes the ganglion cell discharge by 1.8–2.2 ms. Note that ganglion cell impulse activity does not follow the amacrine cell response. Onset of light stimulus occurred before onset of trace. *(c)* Simultaneous intra- and extracellular recordings from nearby on-off ganglion cells. IPSP inverted to depolarizing response by hyperpolarizing current. Onset of ganglion cell impulses and slow rising EPSP have virtually identical latencies. Fast rising, inverted IPSP begins after impulse activity has ceased. Diffuse irradiance: 4.6×10^{-7} W/cm^2 for all traces.

time, and that the peak of the inverted IPSP occurs about 100 ms after the last impulse.

These findings do not support the view that amacrine cells are excitatory to on-off ganglion cells, but are consistent with the model of Fig. 1 as well as

previous work which indicates a chloride-dependent inhibitory relationship between amacrine cells and on-off ganglion cells (Miller and Dacheux, 1976 *b*).

OTHER AMACRINE CELL TYPES On-off amacrine cells generate chloride-dependent on-off IPS responses in on-off ganglion cells (Miller and Dacheux, 1976 *b*). Similar on-off IPSP's, however, were not observed in either on- or off-center ganglion cells, suggesting that the on-off amacrine cells do not interact with these ganglion cell types. Werblin and Copenhagen (1974) have made similar conclusions. If this is the case, what sort of amacrine cell arrangement exists in the on- and off-center channels? In the fish, Toyoda et al. (1973) have described three types of amacrine cells: on-center, off-center, and on-off. This suggests that a type of amacrine cell exists for each of the three types of ganglion cells. Werblin (1970) has suggested that on- and off-center amacrine cells exist in the mudpuppy based on their response pattern to a moving spot. However, stationary illumination of at least some of these cells resulted in on-off responses and it is unclear whether they are similar to the cells described by Toyoda et al. (1973). If such amacrines do exist in the mudpuppy, by feeding back onto bipolar cells and by feeding forward with inhibitory influences on ganglion cells, they could be synergistic to the effects of horizontal cell activity. It is thus possible that on-center, off-center, and on-off ganglion cells are influenced by amacrine cells which have a similar type of receptive field.

OTHER GANGLION CELL TYPES One additional question concerns the organization of ganglion cells which do not show a center-surround antagonistic organization. On cells with "silent surrounds," lacking center-surround excitatory responses, have been described (Miles, 1972; Levick, 1967; Oyster, 1968). In a previous study of mudpuppy ganglion cells (Miller and Dacheux, 1976 *b*) we observed two on cells which did not show surround excitation in response to continuous adaptation of the center and intermittent stimulation with an annulus. This contrasted with the other eight cells for which surround excitation was demonstrated.

Our studies of the preganglion cell retinal neurons revealed 17 cells which could not be identified by the criteria of Werblin and Dowling (1969). These cells, both hyperpolarizing and depolarizing, had some characteristics of bipolar cells but did not show antagonistic center-surround organization. In each case the depolarizing units were chloride sensitive, whereas the hyperpolarizing cells were relatively insensitive to the removal of external chloride. In addition, there was strong evidence for an off-mediated, chloride-dependent IPSP in some of the depolarizing cells. Nelson (1973) has reported depolarizing cells in the mudpuppy which lack antagonistic center-surround organization. He suggested that these cells were bipolars due to the relative depth of recording. We hesitate to accept this method of identification since we have commonly recorded from more than one cell type during a single penetration. This is not unexpected given the relatively large size of mudpuppy neurons and variance in the angle of electrode penetration. Nevertheless the possibility must be considered that ganglion cells which do not show evidence of antagonistic center-surround organization are subserved by equivalent bipolar cell types. Furthermore it is

tempting to think that the silent surround of these cells is mediated by amacrine cells.

In summary the following conclusions are consistent with our studies of the retinal network under chloride-free conditions. *(a)* The separation of on and off pathways begins in the outer retina with two bipolar cell types which respond with opposite polarity changes to light stimulation and are differentially affected by a chloride-free environment. *(b)* The antagonistic surround response of bipolars is mediated by horizontal cells. *(c)* On-center cells are connected to the depolarizing bipolar, off-center to the hyperpolarizing bipolar, and on-off cells receive input from both. Here, the findings suggest that bipolar cells release an excitatory transmitter to both amacrine cells and ganglion cells and that the transmitter is released during periods of relative depolarization. We have no evidence that bipolars are inhibitory. *(d)* On-off amacrine cells receive excitatory input from the depolarizing and hyperpolarizing bipolar cells. On-off ganglion cells receive chloride-dependent IPSP's from the on-off amacrine cells. *(e)* On-center and off-center ganglion cells do not receive inhibitory influences from on-off amacrine cells. *(f)* The hyperpolarization of off-center ganglion cells is a disfacilitatory mechanism and does not depend on chloride.

Finally, our studies using a c-f environment to dissect the retinal network, suggest that there is a difference between outer plexiform layer ionic dependency compared to that of inner plexiform neurons. The outer plexiform layer appears to involve complex ionic mechanisms and at present no single theory seems capable of explaining the ionic basis of neuronal activity of bipolars and horizontal cells. In contrast to this, the inner plexiform layer seems less complex. In this synaptic region the bipolar-cell-mediated influences seem to be excitatory EPSP mechanisms and do not depend on chloride, whereas amacrine cells generate chloride-dependent IPSP's. Thus the view which is compatible with our findings is that the outer plexiform layer in which separation between on and off channels occurs involves complex ionic mechanisms. The interactions at the inner plexiform layer may have a less complicated ionic basis, and in general conform more to the mechanisms described in the central nervous system.

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