Synaptic and Voltage-gated Currents in Interplexiform Cells of the Tiger Salamander Retina

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ABSTRACT We have correlated the membrane properties and synaptic inputs of interplexiform cells (IPCs) with their morphology using whole-cell patch-clamp and Lucifer yellow staining in retinal slices. Three morphological types were identified: (*a*) a bistratified IPC with descending processes ramifying in both sublaminas *a* and *b* of the inner plexiform layer (IPL), and an ascending process that branched in the outer plexiform layer (OPL) and originated from the soma, (*b*) another bistratified IPC with descending processes ramifying in both sublaminas *a* and *b*, and an ascending process that branched in the OPL and originated directly from IPC processes in the IPL, and (*c*) a monostratified IPC with a descending process ramifying over large lateral extents within the most distal stratum of the IPL, and sending an ascending process to the OPL with little branching. Similar voltage-gated currents were measured in all three types including: (*a*) a transient inward sodium current, (*b*) an outward potassium current, and (*c*) an L-type calcium current. All cells generated multiple spikes with frequency increasing monotonically with the magnitude of injected current. The IPCs that send their descending processes into both sublaminas of the IPL (bistratified) receive excitatory synaptic inputs at both light ON and OFF that decay with a time constant of ~1.3 s. Slowly decaying excitation at both ON and OFF suggests that bistratified IPCs may spike continuously in the presence of a dynamic visual environment.

INTRODUCTION

Interplexiform cells (IPCs) have been recognized as distinct cell types for less than two decades (Ehinger et al., 1969; Gallego, 1971). These cells typically have somas in the most proximal stratum of the inner nuclear layer, an ascending process that branches in the outer plexiform layer (OPL), and a descending process that branches in the inner plexiform layer (IPL). The ascending process issues directly from the soma in some species (Boycott et al., 1975) or from the descending process within the IPL in others (Ehinger et al., 1969; Boycott et al., 1975). IPCs receive most of their synaptic input at the IPL while most of the synaptic output from the IPCs impinges upon bipolar cells (Kolb and West, 1977) or horizontal cells (Boycott

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et al., 1975; Dowling and Ehinger, 1975; 1978*a, b*) at the OPL. Recent studies indicate that IPCs also synapse upon rods and cones (Wagner et al., 1988).

The neurotransmitter candidates for IPCs include dopamine in fish (Dowling and Ehinger, 1975) and human (Frederick et al., 1982), glycine in the fish (Marc and Liu, 1984) and tiger salamander (Yang and Yazulla, 1988), GABA in the skate (Brunken et al., 1986) and cat (Nakamura et al., 1980), and somatostatin in the tiger salamander (Li et al., 1986). Dowling and colleagues have described a possible function of the dopaminergic IPC in the fish retina: dopamine increases the responsiveness and reduces the receptive field size of cone horizontal cells (Mangell and Dowling, 1985) by decreasing the conductance of gap junctions between horizontal cells (Lasater and Dowling, 1985; Knapp and Dowling, 1988). Dopamine also increases the conductance of horizontal cells elicited by exogenously applied glutamate (Knapp and Dowling, 1987), the probable neurotransmitter from cones to horizontal cells (Lasater and Dowling, 1982). Zucker and Dowling (1987) have reported that the dopaminergic IPC receives synaptic input from peptide containing centrifugal fibers arising in the olfactory bulb. Also, there is evidence in the *Xenopus* retina that an IPC, which is labeled by both glycine and somatostatin, may stimulate GABA release from horizontal cells (Smiley and Basinger, 1988).

Little information is available about the membrane properties and synaptic inputs to the IPC. Recordings from IPCs in traditional eyecup preparations have been rare. One study in dace (Hashimoto et al., 1980), demonstrated slow potential responses at both light ON and OFF.

Here we used patch recording with Lucifer yellow–filled electrodes in retinal slices (Werblin, 1978) allowing immediate identification of the cell type. So our chances of encountering and identifying IPCs were greatly increased. The patch recordings (Hamill et al., 1981) also revealed the small synaptic and voltage-gated currents that might have been obscured by more traditional recording methods.

METHODS

Ionic Solutions, Staining, and Stimulus

Recordings were made in the retinal slice ~150 μM thick viewed under Hoffman modulation optics as described previously (Werblin, 1978; Maguire et al., 1988). No enzyme treatment was used. Briefly, patch electrodes with resistances of 3–4 MΩ were filled with the following solution (in millimolar): 12 KCl, K-104 gluconate, 1 EGTA, 4 HEPES, 0.1 $CaCl_2$ brought to pH 7.4 with KOH. Bathing solution consisted of: 120 NaCl, 2 KCl, 3 $CaCl_2$, 1 $MgCl_2$, 4 HEPES, 3 glucose brought to pH 7.5 with NaOH.

Steps of full field white light (3 s in duration, luminance = 19 mW/cm^2) were initiated with a shutter upon a photopic background (luminance = 0.76 mW/cm^2).

Cells were stained with Lucifer yellow (1% solution) in the patch electrodes (Stewart, 1978). The stain diffused into the cell and its processes within 3 min, so identification could be made during the recording session. Cells were viewed using a Nikon mercury fluorescent epiilluminator with the B filter package.

Patch Recordings

Recordings were obtained with a List EPC-7 electrometer. Liquid junction potentials of ~ 10 mV, and series resistance, typically ~7 MΩ, were corrected as described in Maguire et al.

(1989). Typical seal resistances were 2–3 GΩ. The data were digitized and stored with an IBM PC/XT using a Data Translation 2800 analog interface board. Analysis was performed using software developed in this lab.

Adequacy of the Voltage Clamp

Since the voltage clamp is performed on IPCs in the slice where their highly branched processes remain intact, it is important to verify that synaptic inputs occurring on the processes are adequately space clamped (Brown and Johnston, 1983). For synaptic currents of 100 pA, a series resistance of 7 MΩ would introduce a voltage error of ~0.70 mV. The space clamp of the synaptic inputs was verified by comparing reversal potentials for the endogenous glutamate input impinging upon the processes and that of kainate puffed directly on the soma. Both the endogenous synaptic current and the puff-elicited current reversed within ±2 mV of 0 mV, suggesting little electrotonic decrement from the recording site at the soma to the processes; therefore the sites of synaptic input were probably adequately clamped for these studies.

RESULTS

Criteria for Identification of IPCs

The large inward sodium current distinguished the IPCs from bipolar cells. This sodium current was measured in every IPC studied. IPCs were tentatively identified by the proximal location of their somata and the wide spread of their processes in the OPL or IPL. Bipolar cells showed no transient sodium current. They typically had a confined spread of processes in the IPL and OPL. Bipolars also often have Landolt's club, although the club was sometimes lost in the slicing procedure. Typical morphologies for Lucifer yellow-stained IPCs and bipolar cells are shown in Fig. 1. Voltage-gated sodium currents were measured in every cell morphologically identified as an IPC, but not in the bipolar cells. Thus a voltage-gated sodium current could be used to distinguish bipolar cells from IPCs. These and other voltage-gated currents in IPCs are described below.

Three Morphological Types of IPC

Three morphological types of IPC were identified (Fig. 2). The type shown in Fig. 2 *A*, which was by far the most frequently encountered IPC (80%, 42 of 52 of the IPCs sampled) sent descending processes into both sublaminas *a* and *b* of the IPL, branching laterally for up to 200 μm. It sent an ascending process into the OPL, arising directly from the soma, which spread laterally in the OPL for up to 200 μM.

The type shown in Fig. 2 *B* was less frequently encountered (12%, 6 of 52 of the sampled cells). It sent its descending processes into both sublaminas *a* and *b*, branching laterally for ~100 μm and more diffusely than the type in Fig. 2 *A*. Its ascending processes arose not from the soma but from the descending processes within the IPL and branched laterally within the OPL for ~100 μm.

The type shown in fig. 2 *C* accounted for only 8% of the sampled IPCs (4/52). It was monostratified, sending its descending process into the most distal stratum of the IPL where it branched laterally for up to 1 mm, much more widely than the branching of the two bistratified types described above. The ascending process of

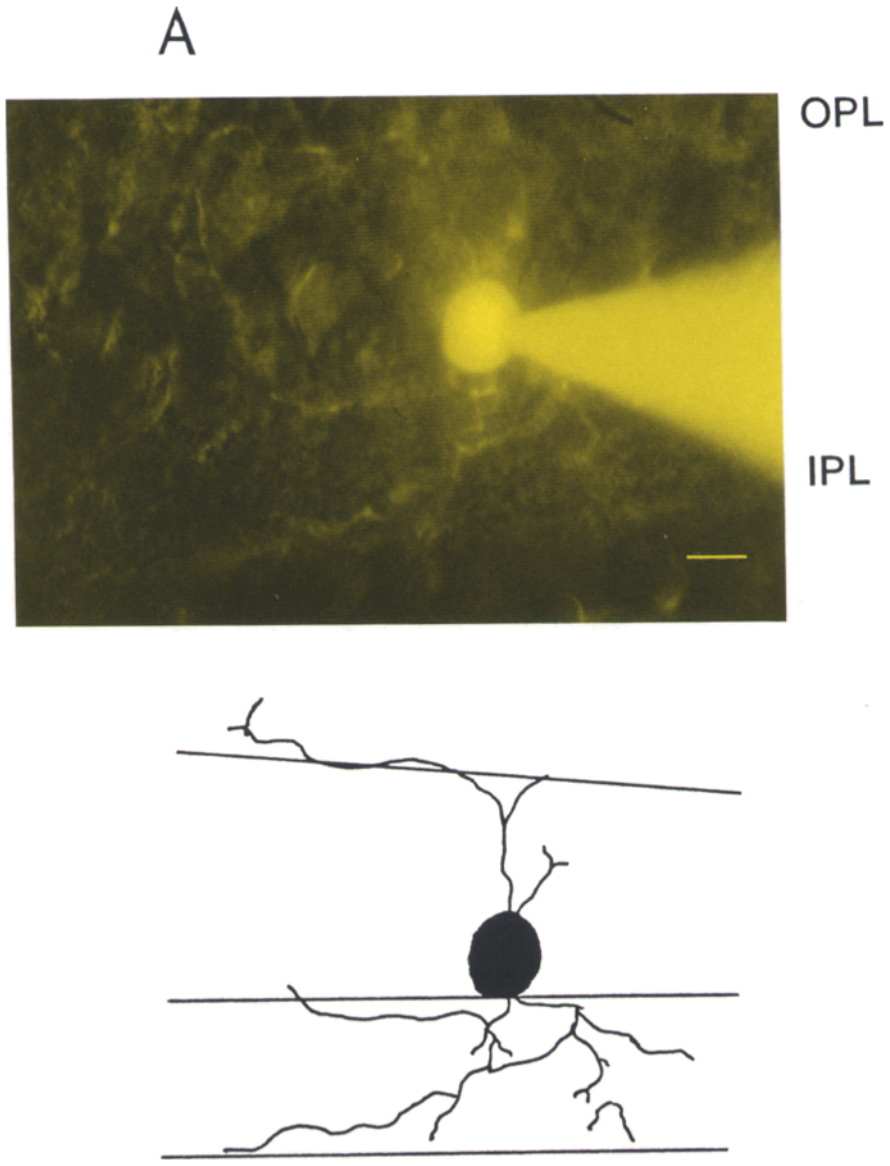

FIGURE 1. Photomicrographs of Lucifer yellow–filled (*A*) IPC and (*B*) bipolar cell in the living retinal slice. The IPC has processes that ramify laterally over large extents, the processes in the IPL ramifying in both the OFF and ON sublaminas, i.e., sublaminas *a* and *b*. The bipolar cell has a narrower spread of processes than the IPC and unlike the IPC a Landolt's club. Scalebars, 10 μm.

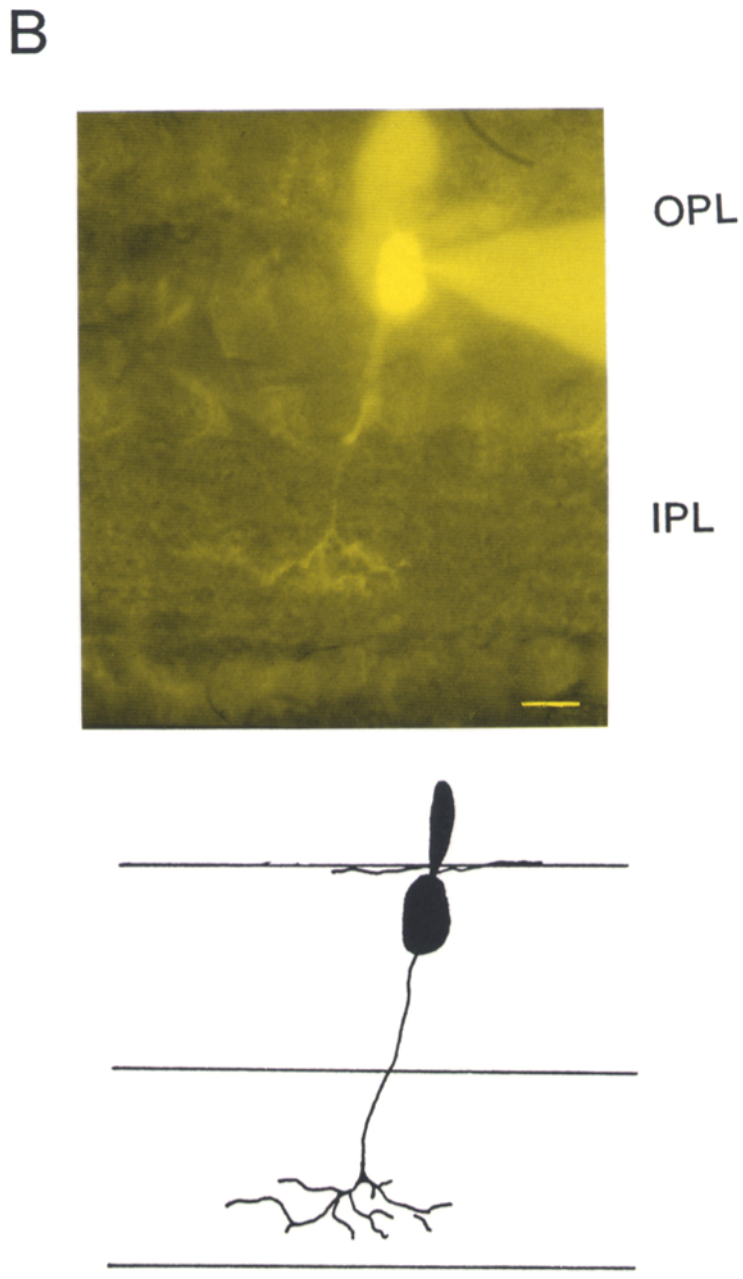

FIGURE 1 (Continued)

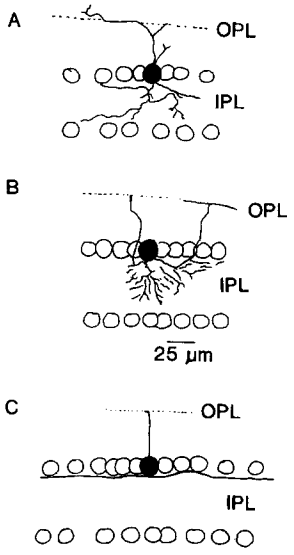

FIGURE 2. Drawings of the three major morphological types of IPC in the tiger salamander retina. (*A*) Bistratified IPC with its ascending processes orginating from the soma. (*B*) Bistratified IPC with its ascending processes originating not from the soma but from its processes in the IPL. These two types are called bistratified because their descending processes extend into both the upper half of the IPL, sublamina *a*, and the lower half of the IPL, sublamina *b*. (*C*) Monostratified IPC sending its descending processes into only the most distal stratum of the IPL.

the monostratified IPC issued directly from the soma and extended into the OPL, but was never seen to branch beyond ~25 μM laterally. However, this process was always very thin and may have been damaged in the slicing procedure, left unstained, or missed because it was too thin to resolve under our viewing conditions.

Synaptic Currents in Bistratified IPCs at Both Light ON and OFF

The light-elicited synaptic inputs to a bistratified IPC are shown in Fig. 3 *A* ($n = 5$). The currents were dominated by excitatory components at both light ON and OFF, and both components reversed at ~0 mV. The relaxation of the currents had a time constant of ~1.3 s. An inward current of ~100 pA was elicited at −70 mV, near the cell's resting potential. Surprisingly, we have not measured any kinetically distinct inhibitory synaptic input elicited by light in these cells, even though preliminary results indicate that exogenously applied GABA and glycine at the IPC dendrites can elicit chloride currents. The light-elicited synaptic current recorded in a hyperpolarizing bipolar cell under the same conditions was sustained, and showed no relaxation (Fig. 3 *B*), quite different from IPC synaptic currents (Fig. 3 *A*).

Whole-Cell Currents

The whole-cell voltage-gated currents of the three IPC types were fundamentally similar (Fig. 4) and are described collectively ($n = 34$). The currents in all three types were quite similar. The major portion of the outward current was nearly sustained, but some IPCs showed a small component of transient inactivation as in Fig. 4, *B* and *C*. All showed a large inactivating inward current and a calcium current described below.

Whole-cell recordings from bipolar cells are shown in Fig. 5 *B*. The outward currents inactivated more rapidly than those of the IPCs with a time constant of ~50 ms. The transient component was inactivated by depolarizing conditioning pulses similar to I_a described previously (Conner and Stevens, 1971). Similar outward currents have been reported in bipolar cells from the retinas of other species (Kaneko and Tachibana, 1985; Tessier-Lavigne et al., 1988).

The transient inward current of the IPC was measured in the presence of extracellular TEA (40 mM) and cobalt (3 mM), and intracellular cesium (116 mM) to block the calcium and potassium currents (Fig. 6 *A*). It was blocked by TTX (0.3 μM;

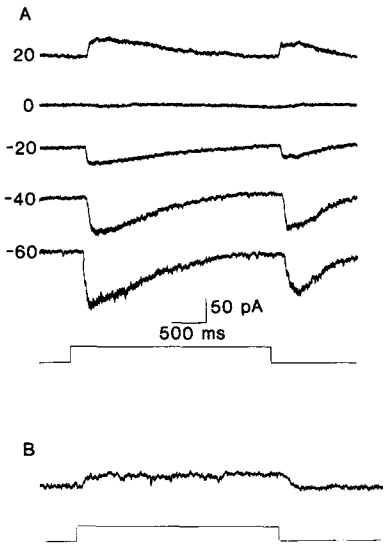

FIGURE 3. (*A*) Synaptic currents in a bistratified IPC elicited by steps of light (stimulus trace is shown at bottom). The membrane was held at the potential as indicated to the left of each current trace. The reversal potential for the components at both light ON and light OFF was ~0 mV, indicating that the synaptic inputs at light ON and OFF were both excitatory. (*B*) Synaptic current in a hyperpolarizing bipolar cell in response to a step of light. Holding potential was −60 mV. E_{Cl} in both cases was near −60 mV.

Fig. 6 *B*), suggesting that the permeant ion is sodium. Activation began at ~−30 mV. This current had a peak amplitude of 5 nA for a step to −20 mV with a time to peak of <200 μs. These characteristics are similar to those for voltage-gated sodium currents of other retinal neurons (Lipton and Tauck, 1987; Lukasiewicz and Werblin, 1988). It is likely that the large amplitude of this current, near 5 nA, coupled with a significant series resistance in the recording, will lead to an error. This current will appear to activate at more negative potentials and the activation range will appear to be narrower than that measured in a well-clamped configuration (Lecar and Smith, 1985).

The slowly activating outward current was blocked by external TEA (40 mM) and internal cesium (116 mM; Fig. 6 *C*). Its amplitude was ~1.5 nA at +10 mV. Outward potassium currents have been reported to be mediated by as many as five different types of K channel (Hoshi and Aldrich, 1988), which are difficult to analyze

with whole-cell current recordings and the characterization of these currents is beyond the scope of this paper. We have not determined that TEA alone will reversibly block the outward current, but Hille (1967) has shown that external TEA blocks a similar current.

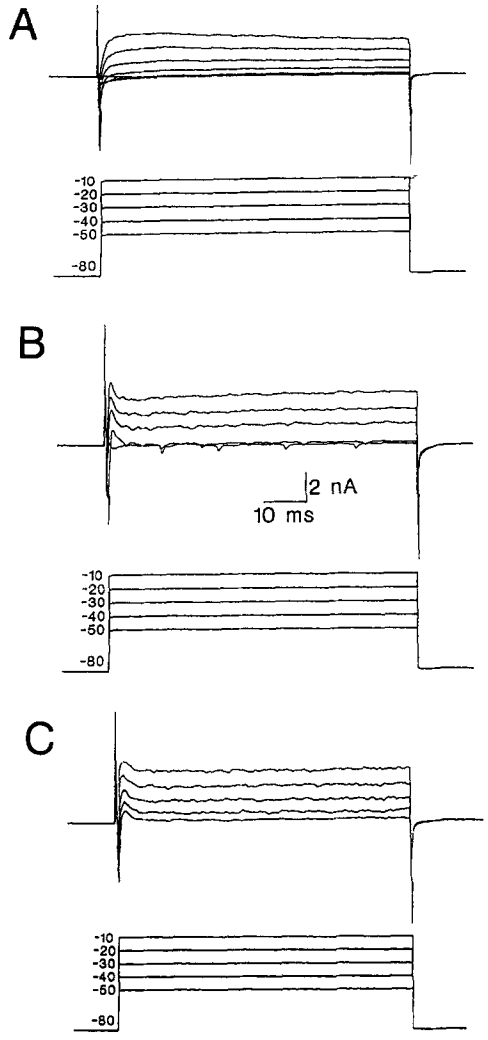

FIGURE 4. Voltage-gated whole-cell currents from the three morphological types of IPC are similar. No consistent differences in the currents were found for the different cell types. Some outward currents contained a small but transient component, but this was not consistent with cell type. (*A*) Whole-cell currents from the bistratified IPC with an ascending process originating from the soma. (*B*) Whole-cell currents from a bistratified IPC with its ascending process originating from the IPL. (*C*) Whole-cell currents from the monostratified IPC.

Voltage-gated L-type Calcium Current

A sustained inward current, probably carried by calcium, was recorded in IPCs shown in Fig. 7 *A*. These currents were revealed by blocking potassium currents with 40 mM external TEA and 116 mM internal cesium. Sodium currents were blocked with 0.3 mM TTX. The calcium current began to activate at ~ -30 mV and

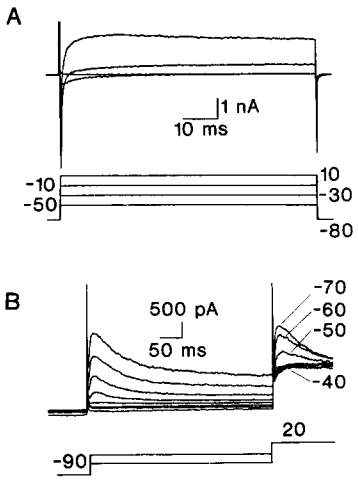

FIGURE 5. Differences in voltage-gated currents in IPCs and bipolar cells. (*A*) Whole-cell currents in IPCs consisted of two obvious components: (*a*) a transient inward current that was blocked by TTX and whose amplitude was reduced by lowering the concentration of external sodium, (*b*) a slowly activating and inactivating outward current that could be blocked by including cesium in the pipette and TEA in the bathing medium. (*B*) Whole-cell currents in bipolar cells consisted of only outward currents. Unlike the IPC, bipolar cells had no transient inward current and their outward currents had a large component, which rapidly inactivated. From a holding potential of −90 mV, conditioning potentials from −80 to +10 mV were presented. The effect of each conditioning potential was tested with a +20-mV step. The outward transient current was fully inactivated by a conditioning potential of −30 mV.

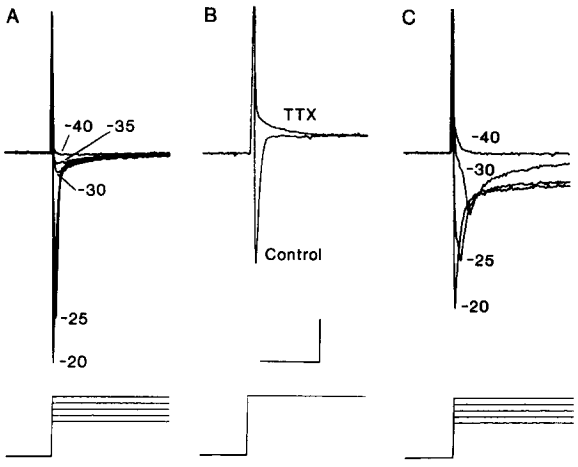

FIGURE 6. Pharmacological separation of the whole-cell currents in IPCs. (*A*) Transient inward current was isolated by using intracellular cesium (116 mM) and extracellular cobalt (3 mM). (*B*) The transient inward current is blocked by TTX (0.3 μM). (*C*) The outward currents alone were blocked by extracellular TEA (40 mM) and barium (10 mM), and intracellular cesium (116 mM) revealing inward sodium and barium currents. Holding potential was −80 mV. Calibrations are 10 ms and 1 nA in *A*, and 10 ms and 500 pA in *B* and *C*.

was maximum near +5 mV as shown in Fig. 7 *C*. This current appears to reverse at +30 mV, a surprisingly negative reversal potential for a calcium current. It is likely that other ions, particularly monovalent cations, flow through the calcium channels, making the apparent reversal potential less positive than conventionally found for calcium currents (Hess et al., 1986).

No transient component was seen in the calcium current at any holding potential between −100 and −30 mV, and holding potentials of −40 mV failed to fully inactivate it. It was blocked by low concentrations of nifedipine (10 μM; Fig. 7 *B*), thus these characteristics suggest that the calcium current in IPCs is similar to the L-type and not the T- or N-types (Fox et al., 1987).

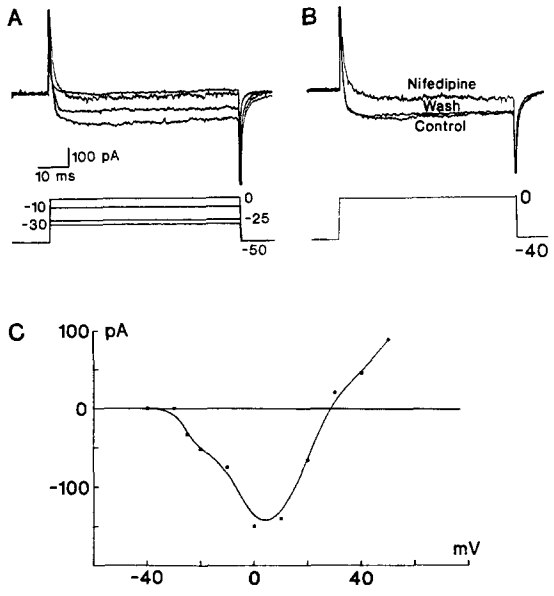

FIGURE 7. Calcium currents in IPCs. (*A*) A sustained inward current (L-type calcium current) was revealed in the IPC by including TTX in the bathing medium to block sodium currents, and TEA in the bath and cesium in the pipette to block the outward currents. (*C*) Calcium current amplitude plotted as a function of test potential. The sustained current activated near −30 mV and reached its maximum inward value near 5 mV. (*B*) This component was reduced in the presence of 10 μM nifedipine, and returned to near control levels with washing. The membrane was stepped to 0 mV from a holding potential of −40 mV.

Current Injection Elicits Continuous and Graded Spiking

The voltage responses to a series of current steps of increasing magnitude are shown in Fig 8. The input resistance of this cell at rest was ~1.5 GΩ so 20 pA of injected current depolarized this cell from −65 mV to ~ −35 mV, eliciting multiple spikes. Larger currents depolarized the cell further but also activated potassium currents as part of the outward rectifier. Therefore disproportionately larger currents were required for further depolarization. The frequency of spiking increased with the amplitude of the injected current and typically reached a maximum frequency of ~15–20 Hz. The amplitude of the synaptic inputs elicited by light stimulation fall into the range of the injected currents, as described above.

Bistratified IPCs Are Sensitive to Kainate

Bistratified IPCs are sensitive to direct application of kainate, an analogue of glutamate, the reported neurotransmitter for bipolar cells (Slaughter and Miller, 1983;

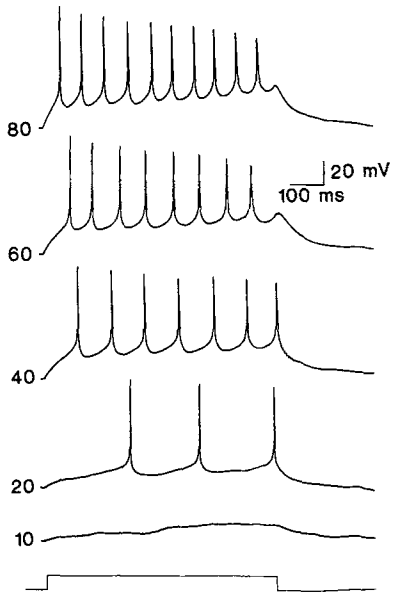

FIGURE 8. Voltage responses to steps of injected current recorded under current clamp. All cells responded with multiple spikes of increasing frequency to current steps of increasing amplitude. The amplitude of the injected current is given to the left of each trace (in picoamperes). The lowest trace shows the time course of the current injection. Large spikes exist here because patch electrodes cause less shunt to the membrane than intracellular electrodes.

Marc, 1988). To eliminate indirect synaptic inputs, the puff was delivered in the presence of cobalt (3 mM), which has been shown to block synaptic transmission in the inner (Schwartz, 1986) and outer retina (Dacheux and Miller, 1976; Ayoub et al., 1988). Kainate was puffed rather than glutamate because kainate is unaffected

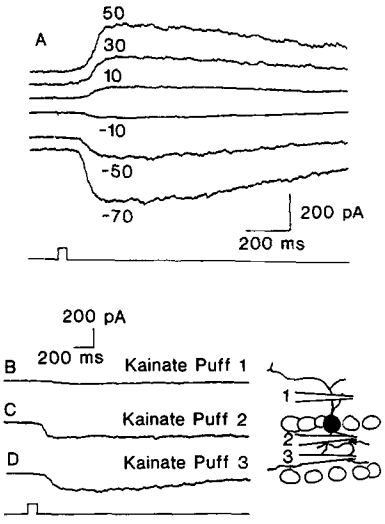

FIGURE 9. Kainate sensitivity of IPCs. (*A*) Response of the bistratified IPC to the direct application of kainate (a glutamate analogue) in the presence of cobalt (3 mM). The values next to each trace indicate the membrane holding potential (in millivolts). The reversal potential for the kainate-elicited current is ~0 mV, which is the same as that for the endogenous excitatory synaptic input. Kainate-elicited currents were demonstrated for application of kainate onto processes of the IPC in sublamina *a* (*C*) and sublamina *b* (*D*), but there is no sensitivity when the kainate was applied 20 μm away from the processes (*B*). The three positions of the kainate-containing pipette in relation to the bistratified IPC are represented in the diagram to the right of the current traces. All currents were recorded from the soma using whole-cell patch clamp.

by glutamate uptake systems so it can be used at lower concentrations and it does not cause receptor desensitization (Trussell et al., 1988).

Fig. 9 *A* shows the response of a bistratified IPC to a puff of kainate (10 μM), a glutamate receptor agonist to which all third-order retinal neurons are sensitive (Lukasiewicz and McReynolds, 1985; Slaughter and Miller, 1983*b*). The kainate-elicited current reversed at ~0 mV, similar to the light-elicited current (see Fig. 3). Kainate sensitivity was present in both the processes that extended into the distal (sublamina *a*) and the proximal (sublamina *b*) half of the IPL (Fig. 9, *C* and *D*).

DISCUSSION

Little is known about the physiological and pharmacological properties of the IPCs because they are difficult to identify during recording in the conventional eyecup preparation. The cells we described here were encountered over a period of three years during the course of other studies. We were able to immediately identify these cells because we routinely use patch electrodes filled with Lucifer yellow (Stewart, 1978). Although each of the components of these studies requires further development, this paper presents a first description of the correlation between morphological and electrical properties of the IPCs and other cells.

Three IPC Types in Tiger Salamander Retina

At least three morphological types of IPC exist in the tiger salamander retina based on the ramifications of their ascending and descending processes and the site of origin of the ascending processes. Only one of each IPC type has been previously shown in any given species (see Dowling, 1988); we show here that all three types exist in the same retina.

Difference between Electrical and Response Properties of IPCs and Other Cells

Although retinal bipolar cells and IPCs both span the region between the OPL and IPL, there are important functional differences. The whole-cell currents of the IPC include a large, transient sodium current (Fig. 5), which is absent from the bipolar cells, whereas bipolar cells have a large transient outward current, which is not apparent in the IPCs (see Fig. 5). Additionally, the excitatory synaptic inputs to the bistratified IPCs occur at light ON and OFF, relaxing at each phase with a time constant of 1.3 s, whereas the bipolar cells receive more sustained excitatory input at light ON or OFF, showing no relaxation during the step of light (see Fig. 3).

Transient amacrine cells (ACs), like bistratified IPCs, branch in both sublaminas *a* and *b* of the IPL and receive excitatory synaptic inputs at light ON and OFF (Maguire et al., 1989). However, unlike the IPCs, the transient amacrine cell responds briefly at light ON and OFF (time constant of relaxation is roughly 100 ms for ACs, but 1.3 s for IPCs). The formation of the brief responses in ACs is probably due to a presynaptic mechanism (Werblin et al., 1988, 1989; Maguire et al., 1989) that is absent in the pathways to the IPCs.

Possible Electrotonic Spread of Potential from the IPC Soma to the OPL

The voltage-gated sodium current in IPCs can be as large as 5 nA, much larger than that reported for amacrine (Barnes and Werblin, 1986; Eliasof et al., 1988) and

ganglion cells (Lukasiewicz and Werblin, 1988). Despite the large size of the current, no spikes either intra- or extracellularly recorded, have ever been reported in regions of the OPL where IPC processes ramify. If the spike propagated from the cell body to the distal processes of the IPC, some form of spike activity should have been measured, even if the recording electrodes didn't penetrate the processes. This suggests that spikes, initiated at the cell body of the IPC, do not propagate to the OPL but are carried there electrotonically.

Hashimoto et al. (1980) have demonstrated that IPCs in the dace retina exhibit slow potentials and some attenuated spiking. We found that all IPCs in the tiger salamander retina exhibit multiple spikes with an amplitude of ~100 mV. The larger spikes reported here may arise because the input resistances of the cells recorded with patch clamp in the present study were typically 1 GΩ or more. Intracellularly

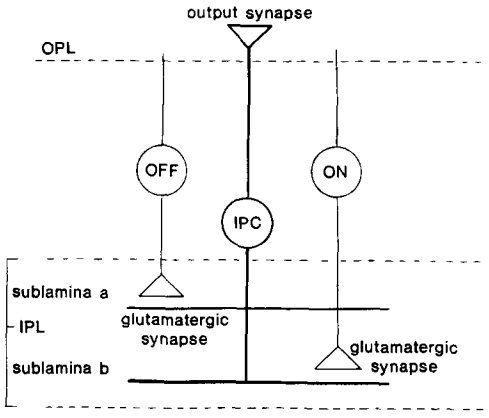

FIGURE 10. Model of the synaptic mechanisms leading to excitation at light ON and OFF in the bistratified IPC. The bistratified IPC sends its descending processes into sublaminas *a* and *b*, where they are probably postsynaptic to excitation from both ON and OFF bipolar cells. There is no evidence for an inhibitory input to these processes. The site of slow inactivation of excitation has not been determined. IPCs could remain depolarized in the presence of a dynamic visual environment. *IPC*, bistratified IPC; *OFF*, bipolar cell that depolarizes to light OFF; *ON*, bipolar cell that depolarizes to light ON; *sublamina a*, distal half of the IPL where the OFF bipolar cells ramify; *sublamina b*, proximal half of the IPL where the ON bipolar cells ramify.

recorded input resistances in earlier studies are typically an order of magnitude smaller, probably due to the shunt produced by electrode penetration.

L-type Calcium Current

We found evidence for the existence of an L-type calcium current (Fox et al., 1987) which has been reported to underly the release of neurotransmitter from synapses in DRG neurons (Holz et al., 1988). We did not determine where the L-channels are located, but the finding that these currents are well clamped suggests that the currents we measure are associated with channels electrotonically close to the recording site at the soma and not at the distal processes, such as that reported in retinal bipolar cell axon terminals (Maple and Werblin, 1986; Maguire et al., 1988).

Bistratified IPCs Receive Slow ON and OFF Excitation

Both ON and OFF inputs appear to converge upon the bistratified IPC. The excitatory input at both light ON and OFF in the bistratified IPC is consistent with the branching of its processes in sublaminas *a* and *b*. These inputs probably arise from bipolar cells: the OFF bipolar cell type would provide sustained excitation to IPC processes in sublamina *a*, and the ON bipolar cells would provide sustained excitation to the IPC processes in sublamina *b* (Hare et al., 1986; Maple and Werblin, 1986) as illustrated in Fig. 10. Surprisingly, we did not measure any light-elicited inhibition in IPCs although preliminary results show a sensitivity to both GABA and glycine at the IPL. In a dynamic visual environment the bistratified IPC may remain tonically active due to these slowly relaxing excitatory inputs at both light ON and light OFF.

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