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Mechanisms of Concerted Firing among Retinal Ganglion Cells

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Summary

Nearby retinal ganglion cells often fire action potentials in near synchrony. We have investigated the circuit mechanisms that underlie these correlations by recording simultaneously from many ganglion cells in the salamander retina. During spontaneous activity in darkness, three types of correlations were distinguished: broad (firing synchrony within 40–100 ms), medium (10–50 ms), and narrow (<1 ms). When chemical synaptic transmission was blocked, the broad correlations disappeared, but the medium and narrow correlations persisted. Further analysis of the strength and time course of synchronous firing suggests that nearby ganglion cells share inputs from photoreceptors conveyed through interneurons via chemical synapses (broad correlations), share excitation from amacrine cells via electrical junctions (medium), and excite each other via electrical junctions (narrow). It appears that the firing patterns in the optic nerve are strongly shaped by electrical coupling in the inner retina.

Introduction

Throughout the brain, the information related to behavior is encoded by the firing activity of local neuronal populations. Our understanding of how these representations are organized derives primarily from a wealth of single-neuron recordings. More recently, it has become apparent that such populations often engage in strong concerted activity patterns that cannot be explained by single-neuron descriptions (Mastronarde, 1989; Krüger, 1991; Abeles et al., 1994). The most prominent of such activity patterns involves synchronous firing within an assembly of neurons. Thus, there has been great interest in the role such synchronous firing patterns play in neural coding, the mechanisms by which they come about, and how they are processed by postsynaptic populations of neurons (Ferster and Spruston, 1995; Singer and Gray, 1995; Meister, 1996).

Retinal ganglion cells fire spikes in response to visual patterns projected on the retina. They can be classified into different functional types, and much is known about how the firing of individual cells depends on the visual input (Stone, 1983; Dowling, 1987). However, multi-neuron recordings have shown that different ganglion cells act in a concerted fashion: nearby cells of similar functional type have a strong tendency to fire in synchrony. This has been observed in many species, including salamander (Meister, 1996), goldfish (Arnett, 1978; Johnsen and Levine, 1983), rabbit (Arnett and Spraker, 1981; DeVries and Baylor, 1996), cat (Mastronarde, 1989), and macaque (E.-J. Chichilnisky, personal communication). Concerted firing is most apparent in the maintained activity during darkness or constant light, when there are no confounding effects of a visual stimulus that might synchronize different cells. Under these conditions, pairs of ganglion cells in the salamander retina can fire synchronous spikes 20 times more frequently than expected by chance. These multi-neuronal firing patterns persist under many types of visual stimulation and can account for a majority of all action potentials recorded from the retina (Meister et al., 1995). Such prevalence of synchronous firing, coupled with indications that subsequent visual stages can specifically detect it (Alonso et al., 1996; Meister, 1996), suggests that correlations among ganglion cells are an important aspect of the retinal code for vision. To further assess what role these synchronous firing patterns play, we sought to determine how they are generated.

Correlated firing can arise from several types of neural circuits, which can be distinguished by the temporal details of the correlations (Gerstein and Perkel, 1969; Aertsen et al., 1989). Two cells might share excitatory input from a third neuron; then, both would tend to fire during the time that the presynaptic cell is depolarized. Alternatively, one cell might excite the other; in this case, the postsynaptic cell would fire systematically with a short delay after the presynaptic spike. Both types of correlation have been observed among retinal ganglion cells (Mastronarde, 1989; Meister et al., 1995). For neurons whose firing rate oscillates periodically, the synchronization could also be achieved by properly timed mutual inhibition (Wang and Rinzel, 1993). However, such oscillatory patterns of activity are rare in the retina and seem to require strong visual stimulation (Neuenschwander and Singer, 1996).

The anatomy of the retina provides several candidate circuits that meet the above criteria (Dowling, 1987; Sterling, 1990; Wässle and Boycott, 1991; Vaney, 1994a). Two ganglion cells can share glutamatergic excitatory input from the same bipolar cell. They may share input from the same photoreceptor through intermediate bipolar cells. Chemical transmission from amacrine cells is generally thought to be inhibitory, but amacrine cells also form gap junctions with ganglion cells through which they may provide shared electrical excitation (Sakai and Naka, 1990; Dacey and Brace, 1992; Dacey, 1993; Vaney, 1994a; Ghosh et al., 1996; Jacoby et al., 1996; Xin and Bloomfield, 1997). Finally, ganglion cells are coupled to each other by gap junctions that may mediate mutual electrical excitation (Sakai and Naka, 1990; Vaney, 1991, 1994b; Dacey and Brace, 1992; Dacey, 1993; Ghosh et al., 1996).

To dissect the contributions of different circuit mechanisms to synchronous firing, we blocked chemical synaptic transmission pharmacologically. This revealed a shared input signal to ganglion cells that relies on chemical synapses. Further analysis showed that this activity arises at least in part from noise in the visual transduction machinery of photoreceptors. In addition, ganglion

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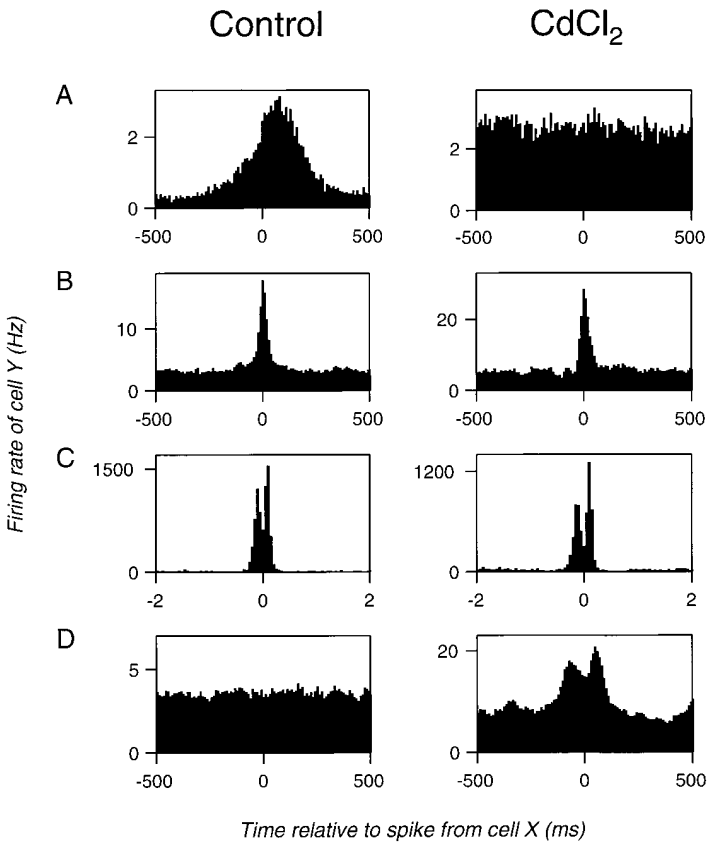

Figure 1. Correlations in Ganglion Cell Firing When Synaptic Vesicle Release Is Blocked

Cross-correlation functions for four pairs of retinal ganglion cells ([A] through [D]). Spike trains were recorded in darkness, first in Ringer's medium (left) and then after addition of 200 μM $CdCl_2$ (right). Note the expanded time scale in (C).

cells receive shared excitation through electrical synapses from a third neuron, most likely an amacrine cell. Finally, ganglion cells are shown to excite each other through electrical junctions. Under certain conditions, this network of coupled ganglion cells sustains patterns of correlated activity spanning large retinal distances.

Results

Correlated Ganglion Cell Firing under Block of Chemical Synaptic Transmission

We recorded spike trains simultaneously from many retinal ganglion cells in the isolated retina of the tiger salamander (see Experimental Procedures). Many of these cells were spontaneously active in darkness. Nearby neurons showed a strong tendency to fire synchronously. One measure of concerted activity between two cells is the cross-correlation function (Figure 1). It represents the firing rate of cell Y as a function of time before or after a spike from cell X. If the two cells were firing independently of each other, this curve should be flat (e.g., Figure 1D [left]). On the other hand, a peak in this curve near zero delay represents an overabundance of synchronous spike pairs (Meister et al., 1995). Figure 1 shows examples of such pairwise correlation functions obtained in a single experiment. Several different time scales for concerted firing are apparent: the precision of spike synchrony is better than 1 ms for the cell pair in Figure 1C, about 10 ms in Figure 1B, and about 100 ms in Figure 1A.

To test the role of chemical transmission in the pathways that generate synchronous firing, we blocked synaptic vesicle release by adding cadmium and removing calcium from the solution (Mittman et al., 1990). Most retinal ganglion cells continued to be spontaneously active; in fact, the firing rates increased by a factor of 2.8 on average (35 cells, two experiments), presumably due to the loss of synaptic inhibition. Some pairs became uncorrelated in their firing (Figure 1A). However, others maintained their synchronous firing (Figures 1B and 1C). Furthermore, some cell pairs that fired independently under control conditions became correlated upon block of vesicular transmission (Figure 1D). Therefore, it appears that some forms of concerted firing are mediated by circuits that do not rely on chemical synapses.

There have been reports of nonvesicular transmitter release in the retina. For example, under certain conditions glutamate uptake mechanisms can operate in reverse (Billups and Attwell, 1996). Since such a transmitter release process would not be inhibited by cadmium, we further added postsynaptic blockers of excitatory neurotransmitters. There was no detectable change in ganglion cell activity from the condition with cadmium alone. Specifically, Figure 2 shows that the pairwise correlations resistant to cadmium persisted when glutamatergic (Figure 2A) or cholinergic (Figure 2B) transmission was blocked postsynaptically. We conclude that these correlations must be mediated by electrical transmission through gap junctions.

To test this notion directly, we attempted to interfere with gap junctional conductance. A number of pharmacological agents have been shown to reduce electrical coupling among neurons—for example, acetate, heptanol, octanol, dopamine, anandamide, and halothane (Lasater and Dowling, 1985; DeVries and Schwartz, 1989; Cook and Becker, 1995; Venance et al., 1995; Yuste et

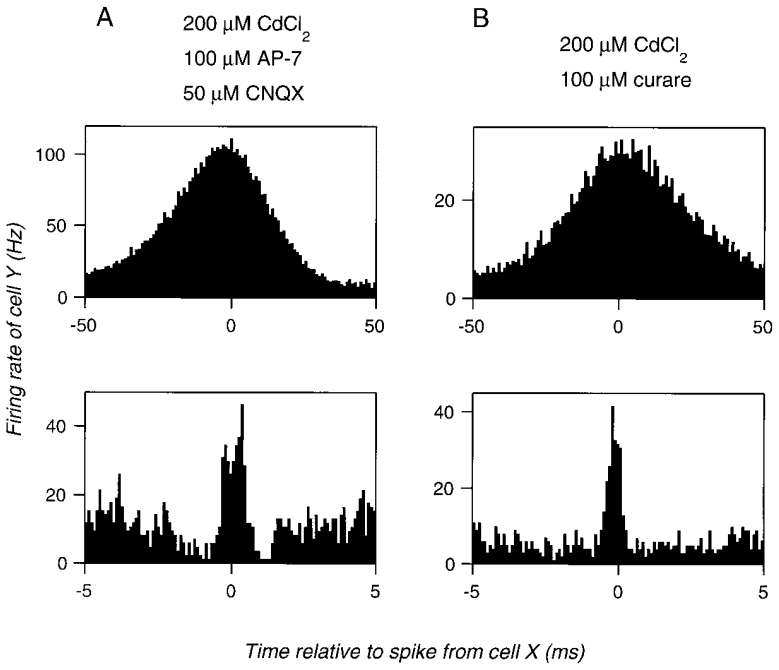

Figure 2. Medium and Narrow Correlations Persist When Excitatory Neurotransmitter Receptors Are Blocked

Cross-correlation functions for four different pairs of ganglion cells recorded in darkness. Presynaptic vesicle release was inhibited with 200 μM $CdCl_2$. In addition, postsynaptic blockers were added for glutamate (A) or acetylcholine (B). Medium- (top) and narrow-width (bottom) correlation peaks were observed under both conditions. Note the different time scales in the top and bottom rows.

al., 1995). Generally, they produce only a partial reduction in junctional conductance and act only on certain types of junctions (Qian et al., 1993; Mills and Massey, 1995). In our experiments, addition of putative blockers to the superfusate did not abolish pairwise correlations (5 mM sodium acetate, 1 mM heptanol, 1 mM octanol, 20 μM anandamide, 0.2% halothane). Many of these are rather nonspecific and have effects on circuitry throughout the retina. For example, addition of 2 mM octanol completely and reversibly silenced all activity among ganglion cells, but as long as the cells were firing, their activity was correlated. However, 0.2% halothane produced a graded decline in the strength of pairwise correlations: the correlation index (see Experimental Procedures) decreased by ~30% for both medium and narrow correlations (155 cell pairs; data not shown). Thus, it is likely that the agents used are only partially effective in blocking ionic flow through gap junctions. Consistent with this notion, tracer coupling between amacrine and ganglion cells in rabbit retina persists even in the presence of putative gap junctional blockers (S. Mills, personal communication).

Three Types of Concerted Firing among Retinal Ganglion Cells

Under control conditions, three types of correlation functions could be distinguished, depending on the width of the central peak: broad (e.g., Figure 1A), medium (Figure 1B), and narrow (Figure 1C). Some cell pairs displayed more than one type of peak superposed. When chemical transmission was blocked, the broad correlations disappeared, but medium and narrow correlations persisted (Figures 1 and 2). To test this initial observation quantitatively, each cross-correlogram from a population of spike trains was fitted by a Gaussian, whose standard deviation was taken to be the correlation width, w (see Experimental Procedures). A histogram of these correlation widths shows three populations (Figure 3): narrow, $w = 0.6 \pm 0.2$ ms (mean ± SD), representing 26% of recorded cell pairs; medium, $w = 34 \pm 11$ ms , 37% of pairs; and broad, $w = 68 \pm 14$ ms, 25% of pairs. Narrow correlation peaks are at least 50-fold sharper than the medium correlations. The width ranges for medium and broad correlations overlap slightly. However, these two types are further distinguished because only broad correlations are abolished by the block of chemical transmission. This suggests that the excitatory signals a ganglion cell receives through gap junctions have a faster time course than those stemming from chemical synaptic inputs.

Previous work has shown that correlated firing is rarely found between an ON-type ganglion cell and an OFF-type cell (Meister et al., 1995). The present report is restricted to OFF cells, which account for ~85% of all cells recorded with the electrode array. Among these, three functional classes can be distinguished by their light response, including one that produces ON/OFF responses to high-contrast flashes (Warland et al., 1997). Concerted firing was not restricted to cell pairs from the same functional class: we found examples of all three modes of concerted firing for any combination of OFF cell classes. Thus, the following analysis will ignore the distinctions among ganglion cell response classes and focus on the differences between the three types of correlations.

Narrow Correlations Reflect Electrical Coupling among Ganglion Cells

As shown above, a significant fraction of cell pairs displayed correlated activity on a sub-millisecond time scale, which was resistant to block of chemical transmission. Often, the cross-correlograms contained two peaks symmetrically spaced a few hundred microseconds from zero delay (Figure 1C). These are most easily explained by mutual excitation between the two ganglion cells through gap junctions. An action potential in one cell would inject charge into the other cell over the

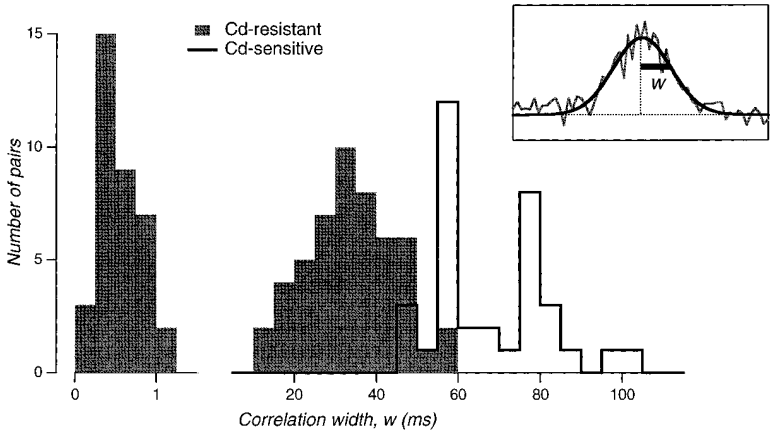

Figure 3. Correlations Occur on Three Time Scales

A histogram of the correlation width, w, of cross-correlation functions during spontaneous activity in darkness (122 cell pairs, two experiments). Each cross-correlogram was fitted by a Gaussian, and w reports the standard deviation (see inset and Experimental Procedures). Correlations that persisted upon addition of 200 μM $CdCl_2$ are shown in gray; others are shown with a black outline. Note the discontinuous time axis.

duration of the spike. If the other cell is poised sufficiently close to threshold, this additional excitation will trigger a postsynaptic action potential. In some cases, the cross-correlograms contained a single narrow peak on one side of zero delay. This might result from an asymmetry in the input impedance or the firing threshold, such that one cell can trigger the other but not vice versa (see Discussion). On occasion, a single peak was centered near zero delay, which could arise if the two cells are electrically coupled to a third spiking neuron that triggers them simultaneously.

To quantitate the strength of this concerted firing, we computed a correlation index: the number of synchronous spike pairs compared to the number expected by chance (Meister et al., 1995; see Experimental Procedures). Figure 4A illustrates this correlation index for all pairs of cells that exhibited narrow correlations (Figure 3). For some nearby cell pairs, the number of synchronous spikes was over 1000-fold greater than that expected by chance. However, at 100 μm distance the correlation index was already much lower. No double-peaked correlations were observed for cell pairs separated by more than 250 μm. This result is consistent with the notion of direct gap junctional coupling between the recorded cells: the dendritic fields of ganglion cells in the salamander retina measure about 220 μm in diameter (Lukasiewicz and Werblin, 1990), which imposes the upper limit for direct junctional connections. At shorter distances, it appears that the strength of electrical coupling increases as dendritic field overlap increases.

Under this hypothesis of mutual electrical excitation, one would expect to find a transmission delay resulting from the time it takes the spike to travel from the first soma up a pre-junctional dendrite and down a post-junctional dendrite to elicit an action potential at the second soma. Figure 4B shows that this is indeed observed. The delay of the peaks in the cross-correlogram increases linearly with the distance between the two cells. The delay ranges up to 1 ms for the most distant cell pairs. A linear fit to the data suggests a propagation velocity of 310 μm/ms. This assumes a straight-line connection between the two cells, and thus the actual propagation along the dendrites is likely faster. The velocity is consistent with active propagation of action potentials into the dendrites, as observed in neocortical pyramidal cells (Stuart and Sakmann, 1994) and recently also in ganglion cells of the rabbit (Velte and Masland, 1997, Soc. Neurosci., abstract). In the unmyelinated axons of these salamander ganglion cells, we previously measured similar spike propagation velocities of ~600 μm/ms (Meister et al., 1994).

The findings in Figure 4 also help in evaluating an alternative hypothesis, namely that the narrow correlations arise from nonspecific (ephaptic) coupling through the extracellular space. Necessary conditions for this are close apposition between ganglion cells X and Y and a restricted extracellular conductance, such that the current flow or potassium released during a spike from X can depolarize Y's membrane without much shunting (Jefferys, 1995). Two OFF-type ganglion cells whose somas are 200 μm apart can approach each other only at the tips of dendrites or if their axons run alongside each other. It is very unlikely that action potentials are transmitted between dendritic tips in the absence of any intercellular junction, given the unfavorable geometry and membrane impedances. Ephaptic coupling has been observed between axons bundled in a nerve, but this is not a viable explanation here, because such an interaction would not be limited to cell pairs of <250 μm intercellular distance (Figure 4A). In conclusion, it appears likely that narrow correlations result from mutual electrical excitation among ganglion cells via gap junctions.

Medium Correlations Are Caused by Shared Electrical Input from Amacrine Cells

The most frequently encountered form of concerted activity consists of synchronous firing on a time scale of 10–50 ms (Figures 1B and 3). These cells often fired brief bursts of spikes whose lengths were similar to the width of the peak in the cross-correlogram (Figure 6B). The peak was generally close to zero delay, so neither neuron had a systematic tendency to fire before the other. This suggests that the two ganglion cells share an excitatory input from a third cell, whose depolarizing influence lasts for about the duration of the bursts. Since these correlations survive the block of chemical transmission, the excitation arrives through gap junctions. The fact that these correlations are so much broader than the sub-millisecond synchronization described

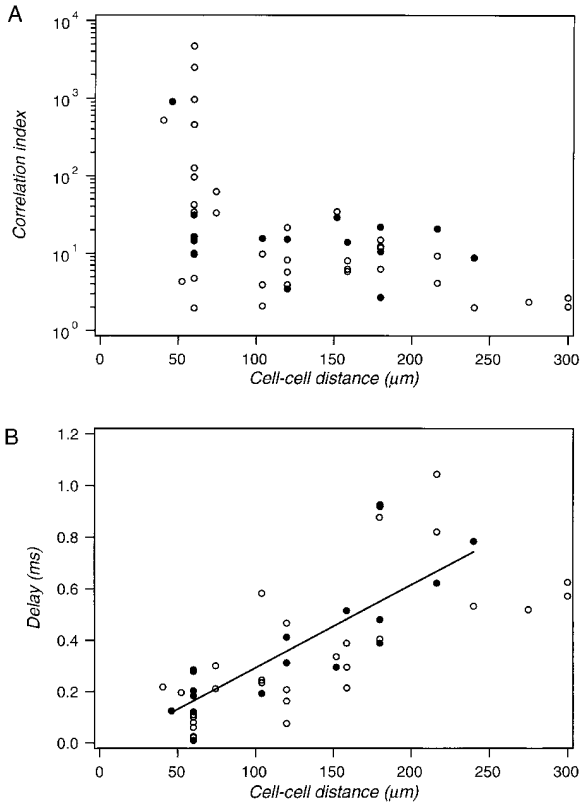

Figure 4. Dependence of Narrow Correlations on Intercellular Distance

(A) The strength of narrow correlations plotted as a function of intercellular distance (52 cell pairs, two experiments). The correlation index was computed for ±1 ms synchrony (see Experimental Procedures). Double-peaked cross-correlograms are marked with closed symbols; these are unambiguously the result of mutual excitation between the two ganglion cells. Single-peaked cross-correlograms are marked with open symbols.

(B) The delay to the peak of narrow correlations plotted as a function of intercellular distance (52 cell pairs, two experiments). The peak position was derived from a Gaussian fit to the cross-correlogram (see Experimental Procedures). Double-peaked cross-correlograms are marked with closed symbols, all others with open symbols. The line shows the best linear fit to the closed symbols with a slope of 310 μm/s.

above could be explained if the presynaptic neuron does not fire spikes, but rather undergoes continuous fluctuations in the membrane potential that last for 10–50 ms. This implicates amacrine cells as the origin of shared activity, since they are the only nonspiking neurons coupled by junctions to ganglion cells (Vaney, 1994a). Some amacrine cells do fire action potentials (Cook and Werblin, 1994) and might serve as the presynaptic source if their gap junctions are much weaker than those producing the narrow correlations above. In that case, a single presynaptic spike would produce only a small postsynaptic effect (see Discussion) and would rarely cause precisely synchronous spikes in the two ganglion cells. A burst of presynaptic spikes, on the other hand, could gradually charge the postsynaptic membrane and produce synchrony on the much longer time scale of the membrane time constant.

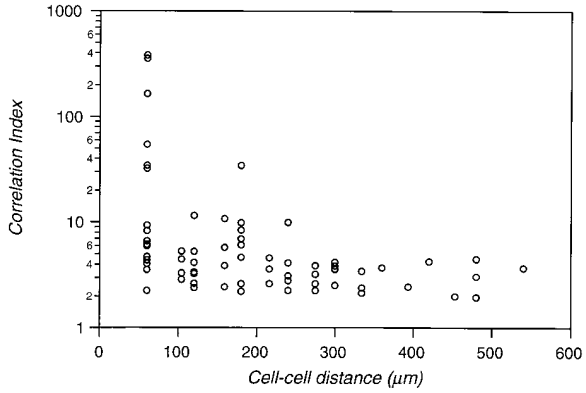

Figure 5. Strength of Medium Correlations Depends on Intercellular Distance

The strength of medium correlations plotted as a function of intercellular distance (67 cell pairs, two experiments). The correlation index was computed for ±20 ms synchrony (see Experimental Procedures).

Thus, medium-width correlations are likely due to shared electrical input from an amacrine cell. Several additional observations support this interpretation. Figure 5 shows the strength of medium-width correlations as a function of the distance between two ganglion cells. Again, the strongest correlations appear at short distances, where the frequency of synchronous firing exceeds chance level 100-fold or more. The correlation index decreases with distance more gradually than observed for the narrow correlations (compare to Figure 4A): significant medium-width correlations are found at separations up to 500 μm. Thus, medium-width correlations do not require overlap of ganglion cell dendritic fields. In the above picture, the dendritic field of the presynaptic amacrine cell serves to provide the shared input.

We tested an alternative hypothesis for the origin of this type of synchrony. Medium- and narrow-width correlations were sometimes observed together, with a sharp peak or double peak superposed on the medium-width peak in the cross-correlogram (Figure 6A). This suggested that they might result from the same kind of process. In particular, cell X might fire a short cluster of spikes. The first spike in that burst produces a synchronous spike in the electrically coupled cell Y. Following this, the membrane dynamics of cell Y dominate to produce its burst of spikes, whose timing is no longer synchronized precisely to the spikes from X. Thus, the narrow correlations would result from the first spike in a burst, medium correlations from subsequent spikes. Figure 6B illustrates that this is not the case. By flagging the incidences of precise synchrony (±1 ms) in two spike trains, we found that they do not systematically fall at the beginning of bursts. One also finds them in the middle of a burst, or at the end, or even among isolated spikes. These temporal relationships are summarized in Figure 6C. For one ganglion cell in the pair, this shows the correlation function between the flagged spikes and all other spikes—that is, the probability of finding another spike at various times before or after a flagged spike. On either side of zero delay, this probability vanishes

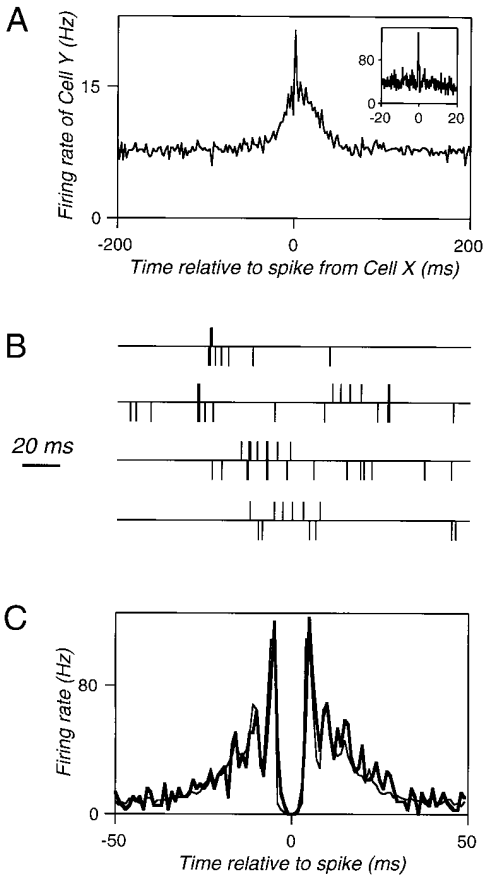

Figure 6. Medium and Narrow Correlations Are Generated Independently

(A) Cross-correlation function for a cell pair synchronized on both medium and narrow (inset) time scales.

(B) Spike trains of two cells X and Y, plotted up and down, respectively. Four segments are illustrated containing brief bursts of firing. Spike pairs that occurred synchronously within 1 ms of each other are drawn in bold.

(C) The auto-correlation function of the spike train from cell X, comparing the mean firing rate of X as a function of time relative to any spike of X (thin line) and relative to spikes that are synchronous with cell Y (thick line).

for a few milliseconds, due to the cell's refractory period (Berry and Meister, 1998). This is followed by a large peak of enhanced firing probability extending to about 30 ms, the approximate duration of spike bursts (Figure 6B). The function is symmetric about the origin, showing that flagged spikes are equally likely at the beginning and at the end of a burst. In fact, the function is indistinguishable in shape from the auto-correlation function of all spikes from this cell. This confirms that the precisely synchronous spikes have no special relationship to the spike bursts that produce the medium correlations. Thus, it appears that narrow and medium correlations result from separate excitatory input signals.

Broad Correlations Originate Partly in Photoreceptors

The medium and narrow correlations do not require chemical transmission, and thus the source of these excitatory signals must lie in the inner retina, among amacrine and ganglion cells. By contrast, broad correlations require at least one chemical synapse. Thus, the shared input signal may originate in the outer retina and be transmitted to both ganglion cells via bipolar cells. Some of the spontaneous ganglion cell firing observed in darkness is caused by fluctuations within photoreceptors, such as thermal activation of the visual pigment molecules (Barlow et al., 1971; Baylor et al., 1980; Aho et al., 1988). It has been suggested that these signals produce correlated firing among ganglion cells whose receptive fields share the same photoreceptors (Arnett and Spraker, 1981; Mastronarde, 1983b). To test this notion, we determined how the broad correlations vary with light intensity. It is well known that the time course of phototransduction in the rod outer segment speeds up in the presence of background light (Baylor et al., 1979; Pepperberg et al., 1994). Under these conditions, each spontaneous transduction event would cause a shorter burst of spikes in the ganglion cells. If these events are shared between two ganglion cells, one thus expects a sharpening of the pairwise correlation function. This was indeed observed. Figure 7 shows that for many ganglion cell pairs exhibiting broad correlations, the width of the correlation peak was reduced in the presence of a constant dim adapting light. This suggests that at least some of the broad correlations derive from fluctuations in photoreceptors.

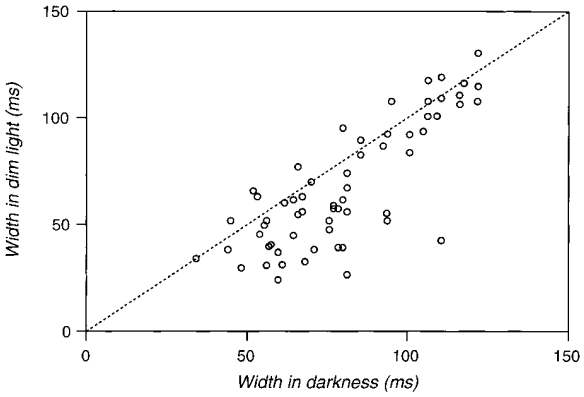

Figure 7. Broad Correlations Sharpen under Constant Illumination

Spontaneous activity was recorded first in darkness, and then under constant dim illumination (720 isomerizations/rod/s), and finally under synaptic block with 200 μM $CdCl_2$. Cross-correlograms were computed for all cell pairs, and broad correlations were identified by their cadmium sensitivity. For these cell pairs, the width of the cross-correlogram peak in dim light is plotted against the width in darkness.

Electrical Coupling Sustains Propagating Waves of Activity in the Ganglion Cell Population

Two cells that fired independently of each other under control conditions often showed strong correlations when chemical transmission was blocked (Figure 1D). These cross-correlation functions generally contained two peaks equally spaced symmetrically on either side of zero delay. Thus, the two cells tended to fire with a delay—typically tens of milliseconds—but either cell was equally likely to fire before the other. Closer inspection showed that this delay increased proportionally to

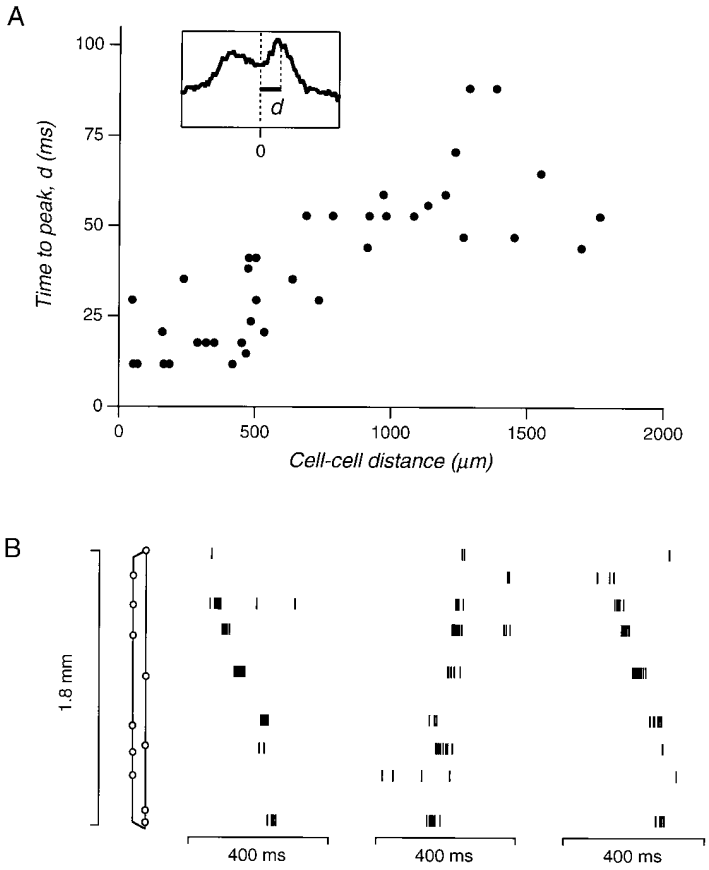

Figure 8. Propagating Bursts of Activity during Block of Chemical Transmission

(A) "Induced" cross-correlation functions have peaks symmetrically placed from zero delay. The time to peak (see inset) is plotted against the intercellular distance on the retina.

(B) Propagating bursts of activity. Eleven cells were recorded using a linear electrode array, and their locations are marked with open circles on the array outline (left). Each spike train is plotted with the vertical offset corresponding to the cell location. Three brief episodes are shown containing bursts of spikes propagating in either direction.

the distance between the two cells (Figure 8A). Furthermore, these "induced" correlations were seen at intercellular distances up to 1.8 mm, the largest separation observable with the electrode array. This suggested that neural activity might propagate across the retina. A wave of excitation might travel across the tissue in one direction, triggering cell X before cell Y, and later return in the other direction, triggering cell Y before cell X. In fact, such traveling bursts of activity were observed directly, as illustrated in Figure 8B.

One would expect that such waves of excitation should travel in all possible directions, not only along the line of separation between the two ganglion cells that happen to be observed. In particular, a wave traveling perpendicular to this line of separation should reach both cells at the same time. Thus, one should observe all possible values of firing delays, from zero up to the maximum given by the ratio of cell separation and wave velocity. However, simple geometrical considerations (Figure 9A; Experimental Procedures) show that large delays are far more frequent than short ones, which can explain the double-peaked correlation functions.

To pursue this hypothesis further, we analyzed a simple model of such activity patterns (Figure 9A): a linear wave of width h travels across the retina at constant velocity. Cells fire at a high rate within the wave and at a low rate outside the wave. Waves travel in all directions with equal probability. With these assumptions, one can derive the shape of the cross-correlation function for any intercellular separation (Experimental Procedures). These predictions match the observed cross-correlations very well (Figure 9B). From an analysis of 33 cell pairs, we estimated the average width of the traveling waves at $h = 0.69 \pm 0.04$ mm (mean $\pm$ SEM) and the average velocity at $v = 15.0 \pm 0.5$ mm/s. Note that these waves can cross the entire salamander retina in 0.3 s and thus propagate 100-fold faster than the traveling excitations previously observed in developing retina (Meister et al., 1991). This velocity cannot be explained by extracellular diffusion of an excitatory substance, such as potassium ion. Furthermore, the waves clearly do not rely on chemical synaptic transmission. Thus, they appear to propagate through the electrically coupled network of ganglion and amacrine cells.

Discussion

Three Mechanisms Contribute to Concerted Firing

At least three different circuits are responsible for correlations in the firing of salamander retinal ganglion cells. Synchronous firing with sub-millisecond delays appears to be caused by electrical coupling among ganglion cells (Figure 10A). A spike in one cell injects charge into the other cell, sufficient to drive its membrane potential across threshold for spike generation. Such interactions were seen only at short distances where the two dendritic fields overlap. The connection may be established by gap junctions between dendrites.

Correlations of medium width, with synchrony on the 10–50 ms time scale, are also due to electrical transmission. However, they derive from shared input to the two ganglion cells from a third neuron, whose fluctuations

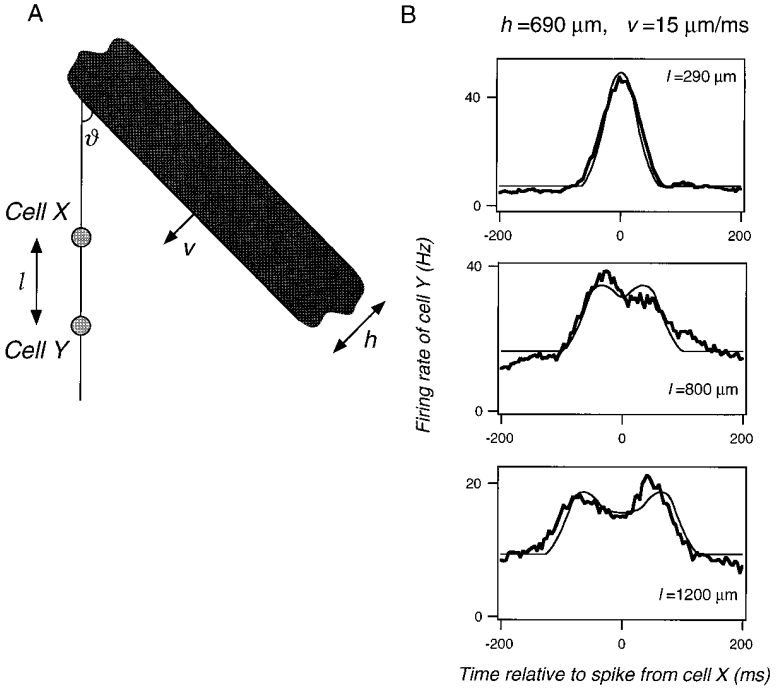

Figure 9. Cross-Correlograms Predicted From Propagating Waves of Activity

(A) Geometry of the model: the two recorded cells are separated by a distance l, and a stripe of excitation of thickness h travels with velocity v at an angle ϑ relative to the line of separation. This model yields a prediction for the cross-correlation function between the two spike trains (see Experimental Procedures).

(B) Examples of observed (thick line) and predicted (thin line) cross-correlation functions for three cell pairs at different distances. Spike trains were recorded before and after addition of 200 μM cadmium, and 33 cell pairs with induced correlations were identified. The predictions shown here were generated using the average values for v (15 mm/s) and h (0.69 mm) derived from all 33 correlation functions.

in membrane potential transiently depolarize both recorded ganglion cells (Figure 10B). This shared input neuron may be a nonspiking amacrine cell or a cell that fires in bursts but has only weak electrical connection to the ganglion cells. Such correlations account for the bulk of concerted activity we reported previously (Meister et al., 1995).

Broad correlations, on a time scale of 50–100 ms, are also due to a shared input signal, but it reaches the ganglion cells by a pathway including at least one chemical synapse. Part of this signal originates in photoreceptors as noise in the visual transduction reactions (Figure 10C). Other contributions might come from fluctuations in bipolar cells (Maple et al., 1994).

The three different time scales for ganglion cell correlations in the salamander retina have a striking parallel in previous reports from the cat retina (Mastronarde, 1989). Our present work helps interpret those observations by specifying the underlying circuitry. From pairwise recordings and stimulation of cat ganglion cells, Mastronarde identified three types of events that synchronized their firing in darkness or constant light. First, direct excitatory interactions between ganglion cells lasted 0.5–1 ms (Mastronarde, 1983c). Based on their short latency and duration, Mastronarde speculated that they result from gap junctions. The present pharmacological results confirm this proposal. Second, a fast shared input produced correlations on an intermediate time scale of 2–10 ms (Mastronarde, 1983a), somewhat faster than the corresponding medium correlations in the cold-blooded salamander retina. Each such spontaneously active input signal was excitatory to ON cells and at the same time inhibitory to OFF cells or vice versa. Our results suggest that amacrine cells are the source of this activity and how the reciprocal influences might be achieved: ON-type amacrine cells could excite ON ganglion cells through gap junctions and inhibit OFF ganglion cells through chemical synapses; OFF-type amacrines with the opposite wiring would provide the complementary input signal. The difference between electrical excitation and chemical inhibition also explains Mastronarde's observation that the excitatory effects of these inputs were more short-lived than the inhibitory effects. Third, a slow shared input accounted for correlations with a width of 40–50 ms (Mastronarde, 1983b). This was traced to single quantal events in rod photoreceptors, since the rate of these events in dim light matched the calculated rate of photoisomerizations. Although this was not mentioned by the author, these correlations also sharpened with increasing light level (see Figure 1 of Mastronarde, 1983b), as observed for broad correlations in the present work. In summary, the remarkable similarity between concerted firing in salamander and cat suggests that the three pathways in Figures 10A–10C are part of the basic circuit plan of the vertebrate retina.

Electrical Excitation in the Inner Retina

These proposed circuits include a remarkable degree of electrical coupling both among ganglion cells and between ganglion and amacrine cells. In recent years, anatomical evidence has mounted that ganglion cells are connected to each other and to certain amacrine cells (Vaney, 1991, 1994a; Dacey and Brace, 1992; Dacey, 1993; Cook and Becker, 1995; Ghosh et al., 1996; Jacoby et al., 1996; Xin and Bloomfield, 1997). These conclusions are based on the spread of small-molecule tracers from an injected ganglion cell to other neurons. Direct proof that these connections also provide a significant electrical conductance has been difficult to obtain. In experiments using two intracellular electrodes, Sakai and Naka (1990) showed that electric current passed

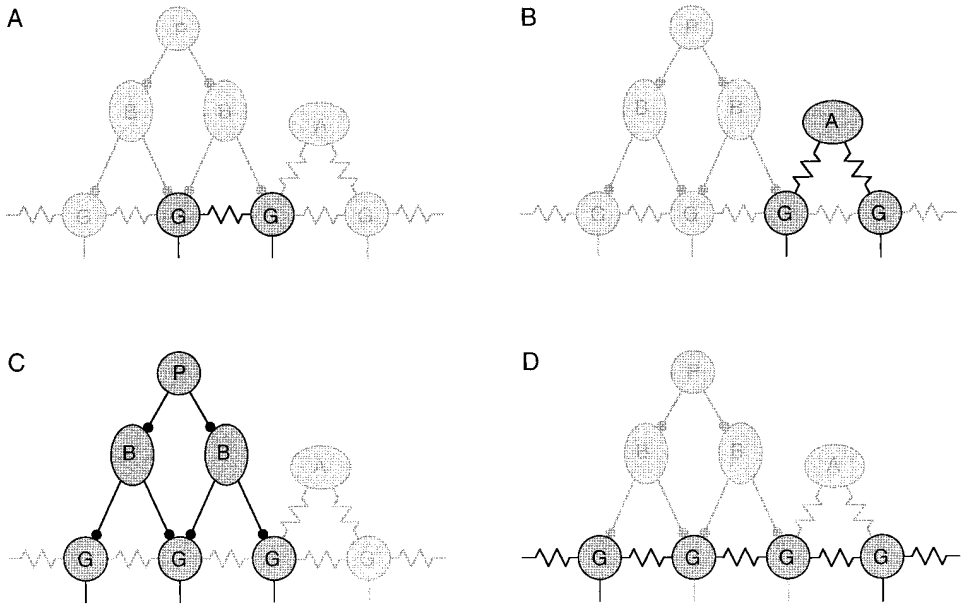

Figure 10. Schematic of Mechanisms Underlying the Correlated Activity of Retinal Ganglion Cells

(A) Narrow correlations are caused by direct gap junctional coupling of spiking neurons.

(B) Medium correlations result from gap junctional connections to a third neuron such as an amacrine cell.

(C) Broad correlations are the result of common chemical inputs from slow neurons such as photoreceptors or bipolar cells.

(D) Waves of activity under chemical synaptic block are due to remote connections through a network of electrically coupled cells.

between nearby ganglion cells and also from amacrine to ganglion cells. The measurements were plagued by a substantial leak current and could not determine the absolute conductance of this intercellular junction. Thus, it is important to consider whether electrical coupling through gap junctions can, at least in principle, produce the observed correlations among ganglion cell spike trains.

Consider a salamander ganglion cell Y with an input conductance at the soma of $G_i = 1000$ pS, a membrane time constant of $\tau = 40$ ms, and a capacitance of C = 40 pF, as measured in a retinal slice preparation (Taylor et al., 1996). Assume that half of the resting conductance is due to a gap junction with a neighboring ganglion cell X, with a conductance G = 500 pS; note that this represents only 1% of the conductance of horizontal cell junctions (McMahon et al., 1989; Lu and McMahon, 1996). When cell X fires an action potential of amplitude V = 100 mV and duration $\Delta t = 1$ ms, a current $I = V \cdot G$ flows through the junction into cell Y. This deposits a charge $Q = \Delta t \cdot V \cdot G$ onto cell Y's capacitance C, such that its membrane potential increases by a step of $\Delta V = \Delta t \cdot V \cdot G/C = 1.25$ mV. After the spike, this voltage decays back to the resting potential with the membrane time constant τ.

Clearly, the post-junctional cell must already find itself close to the firing threshold, such that a 1 mV step can trigger an action potential. Nearby ganglion cells of the same type often have overlapping receptive field centers and thus will share sources of excitatory input. In fact, ganglion cell pairs with narrow correlations often show medium or broad correlations as well (Figure 6A). Through these shared inputs, the two cells will occasionally be brought near threshold at about the same time, such that when the first cell fires, the small postsynaptic pulse from electrical transmission can be sufficient to trigger the other. Still, we found that the spikes paired with sub-millisecond synchrony are rare and constitute only a small fraction of each cell's spike train: on average, 8.1% of 61 cells are involved in narrow correlations. In cat retina, Mastronarde (1983c) estimated that a Y cell action potential causes a spike in a coupled Y cell with a probability of only 1%–4%.

Several unknown factors can affect the above calculation in either direction. If the junction is located on a dendrite of cell X, and dendritic conduction is passive, then the spike amplitude may decay along the dendrite and produce a smaller voltage step in cell Y. On the other hand, recent work suggests that somatic spikes propagate actively into the dendrites of rabbit ganglion cells (Velte and Masland, 1997, Soc. Neurosci., abstract), which would maintain the efficacy of such a connection. If the junction is located on a dendrite of cell Y, the voltage step in the dendrite would be greater than estimated above, since only the local dendritic capacitance must be charged. If dendrites can initiate spikes that propagate to the soma, this would boost the efficacy of electrical coupling.

For the shared input signal that produces the medium correlations, electrical transmission appears far more favorable. This input varies much more slowly than an action potential, and thus the post-junctional membrane integrates the current over time. For fluctuations in the voltage of X that last longer than the membrane time constant of Y, the post-junctional signal is simply given by the ratio of junctional to total conductance $\Delta V \approx V \cdot G/G_i$. As above, this is subject to possible electrotonic decay along dendrites. Consistent with this expectation,

the shared excitatory events underlying medium correlations have a much greater effect on the concerted activity among ganglion cells. In fact, they account for almost all of the spontaneous activity of certain salamander ganglion cells, and for ~50% of all spikes recorded by the electrode array, even under visual stimulation (Meister et al., 1995). In cat retina, these shared inputs cause ~80% of the spontaneous firing of Y cells (Mastronarde, 1983a). Thus, a significant portion of the excitatory input to ganglion cells may arrive through electrical synapses from amacrine cells and other ganglion cells, rather than via chemical synapses from bipolar cells (Sakai and Naka, 1988).

Spontaneous Firing and the Importance of Synaptic Inhibition

When all chemical transmission is blocked, the inner retina is still spontaneously active, though it presumably receives no input from the outer retina. This could be understood if there is a type of neuron whose remaining membrane conductances are biased to produce a net depolarizing current, such that the membrane potential crosses firing threshold spontaneously. After a brief burst (Figure 6B), a hyperpolarization might ensue, followed by renewed charging of the membrane to threshold. However, these cells do not operate in isolation but are coupled laterally, and this clearly shapes their patterns of activity.

When observing an entire population, we found spontaneous waves of ganglion cell firing, propagating across the retina in various directions. Presumably, the excitation is transmitted through the electrically coupled network of ganglion cells, maybe involving the coupled amacrine cells as well (Figure 10D). In a simple picture of this domino effect, a row of ganglion cells fires, exciting the cells to which they are coupled, which in turn fire and excite their neighbors. Note that a single spike can trigger a ganglion cell 100 μm distant in 400 μs (Figure 4B), so one might expect this wave to propagate at 250 mm/s. However, as discussed above, these trigger events are rare and apparently insufficient to sustain a regenerative wave. Instead, the ganglion cell must integrate excitation from its neighbors for some time before it is reliably led to fire. This is why the wave propagates at only 15 mm/s (Figure 9B). Since direct coupling among ganglion cells extends to about 250 μm (Figure 4A), each ganglion cell receives spikes from its neighbors for about 17 ms before it begins firing. In this view, the velocity of the wave should decrease if one raises the firing threshold of the ganglion cells. Eventually, a point will be reached where the integration time required to reach threshold exceeds the membrane time constant: then all propagating activity stops.

Under normal dark conditions, this quiescent state of the ganglion cell network is likely maintained by inhibition from chemical synapses, as suggested by two observations. First, the net effect of blocking chemical transmission was excitatory, raising the steady firing rates of most ganglion cells; thus, tonic inhibition outweighs excitation through chemical synapses. Second, the addition of picrotoxin, a blocker of GABAergic transmission, by itself induced propagating bursts of activity (data not shown). Thus, the inhibition that ganglion cells receive from amacrine cells has an important damping role: to keep the ganglion cells from exciting each other and losing track of their visual processing task.

Retinal Processing

What is the importance of electrical coupling for visual processing? On one level, our results show that electrical coupling is directly responsible for much of the concerted firing among ganglion cells. In particular, the prominent medium-width correlations between the spike trains of ganglion cells are a consequence of divergent connections from individual amacrines to several ganglion cells. As discussed previously, the coincidence of ganglion cell spikes on this time scale marks the activity of the shared amacrine cell and conveys this information through the optic nerve through a concerted firing pattern (Meister et al., 1995; Meister, 1996). Whether this distributed signal is recognized and interpreted by the brain still remains to be seen.

More fundamentally, these observations—together with the solid anatomical evidence for gap junctional coupling—imply that amacrine cells are excitatory to ganglion cells and that this input is strong enough to account for a good fraction of the output of certain ganglion cell types. This should revise the common view of amacrine cells as inhibitory interneurons, a notion based on the fact that almost all amacrine cell types contain inhibitory chemical transmitters (Vaney, 1990). The same amacrine cell may exert both excitation and inhibition, possibly on different targets and with different dynamics, as suggested above in explaining medium-width correlations in cat retina. Vice versa, a ganglion cell could receive both fast electrical excitation and delayed chemical inhibition; this may help produce the transient light response of cat alpha cells, which seem particularly well coupled to amacrines (Vaney, 1991) and show a strong component of medium-width correlations (Mastronarde, 1983a). Generally, the prominence of electrical excitation in the inner retina suggests that the amacrine cells—the most diverse of retinal populations—may take a much more active part in shaping ganglion cell responses rather than merely specifying when the ganglion cell should remain quiet.

The electrical coupling between ganglion cells plays a different role: it necessarily leads to some lateral averaging of visual signals. The combination of local excitation among ganglion cells and broad lateral inhibition from amacrine cells could produce a spatial bandpass filter for the neural image. This is analogous to the network of coupled photoreceptors and inhibitory horizontal cells in the outer retina, but the active membranes of ganglion and amacrine cells can convey more nonlinear properties to this filter. For example, a local group of ganglion cells may all fire synchronously if the visual stimulus matches the properties of the filter but not at all if the match is poor. As elsewhere in the retina, this electrical coupling is likely under modulatory control (Cook and Becker, 1995), which may adapt the spatial filter to different needs. Such a change in lateral coupling should lead to pronounced changes in the receptive fields of individual cells. For example, alpha ganglion

cells in the light-adapted cat retina have receptive field centers that approximately match their dendritic fields in size. However, in darkness the receptive field center expands up to 2.8-fold (Peichl and Wässle, 1983). This could be explained if alpha cells are coupled to each other and the strength of the coupling decreases with light adaptation. More generally, such modulation would alter the balance between excitation and inhibition in the inner retina and thus exert a strong effect on the responses of individual ganglion cells as well as their patterns of concerted activity.

Experimental Procedures

Preparation and Recording

Larval tiger salamanders (*Ambystoma tigrinum*) were dark adapted for at least 30 min and then decapitated and pithed under dim red light. The retina was isolated under infrared illumination into Ringer's medium (110 mM NaCl, 2.5 mM KCl, 1 mM $CaCl_2$, 1.6 mM $MgCl_2$, 10 mM D-glucose, 22 mM $NaHCO_3$ [pH 7.4]) aerated with 5% CO_2/95% O_2. A piece of retina 2–3 mm in diameter was placed ganglion cell–side down on a multi-electrode array, and the action potentials of ganglion cells were recorded and sorted as described (Meister et al., 1994). Some additional safeguards were taken in identifying spikes from neurons that appeared to fire with sub-millisecond synchrony: such cell pairs were analyzed only if they could be recorded on separate electrodes, avoiding the complications resulting from temporal overlap of different action potential waveforms. To further ensure that these were not two recordings of the same spike, we required that there be occasions where either cell fired without the other. For each identified neuron, these procedures yielded a continuous spike train throughout the duration of the experiment and an estimate of the location of the cell body over the electrode array. In this way, we monitored simultaneously 20–50 neurons for up to 6 hr. Results presented here derive from six such experiments.

To block vesicular transmitter release, 200 μM $CdCl_2$ was added to the solution flowing through the recording chamber, and $CaCl_2$ was replaced by $MgCl_2$. Control experiments showed that 20–200 μM $CdCl_2$ eliminated all light responses in ganglion cells. Still, this might be caused by a synaptic block in the outer retina, which is in more intimate contact with the superfusate. To fully ensure that cadmium had access to release sites near the retinal ganglion cells, we sometimes bathed the retina in medium containing $CdCl_2$ for 30 min before placing it on the electrode array. The effects on ganglion cell firing were indistinguishable from delivery by superfusion. Further evidence that drugs can access ganglion cells even when delivered from the photoreceptor side comes from experiments with 1 μM tetrodotoxin: ganglion cell firing stopped within minutes of the onset of superfusion (Meister et al., 1991).

Postsynaptic blockers were added from stock solutions to the superfusate just prior to the experiment: 2-amino-7-phosphonoheptanoic acid (AP-7), 100 μM; 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), 50 μM; and tubocurarine chloride (curare), 100 μM (all from Research Biochemicals). Octanol was first dissolved in dimethylsulfoxide (DMSO) to yield final concentrations in Ringer's of 1 mM octanol and 0.1% DMSO. In control experiments, 0.1% DMSO by itself had no effect on ganglion cell light responses or maintained activity. Halothane was added to the superfusate at 0.2% v/v.

Visual stimuli were presented from a computer monitor projected onto the photoreceptor layer (Meister et al., 1994). Spatially uniform, square-wave steps of light served to distinguish ON- and OFF-type ganglion cells and to ascertain the loss of light responses under synaptic block. ON-type ganglion cells were recorded only rarely (Warland et al., 1997) and therefore were excluded from this analysis. Firing correlations were assessed either in darkness or under constant illumination with dim white light (720 isomerizations/rod/s).

Analysis of Neural Spike Trains

The cross-correlation function between two spike trains was computed by histogramming all time differences between a spike from one cell and a spike from the other cell (Meister et al., 1995). When the cross-correlogram showed a single peak near zero delay, it was fit by a Gaussian curve of the form

$R^{(XY)}(t)$ = firing rate of cell Y at time t relative to a spike from cell X:

$$\approx b + a\cdot\exp\left(-\frac{(t-d)^2}{2w^2}\right)$$

where b = baseline firing rate, a = amplitude of peak, w = width of peak, and d = delay of peak. For correlograms with two symmetric peaks on either side of the origin, the fit was restricted to one peak.

To evaluate the strength of a pairwise correlation, the "correlation index" was computed as the ratio between the number of spike pairs that occurred within $\pm\Delta t$ of each other and the number of such spike pairs expected by chance, based on the cells' average firing rates (Meister et al., 1995):

$C^{(XY)}$ = correlation index between cells X and Y

$$= \frac{\int_{-\Delta t}^{+\Delta t} R^{(XY)}(t)dt}{2\cdot\Delta t\cdot R^{(Y)}}$$

where $R^{(Y)}$ = average firing rate of cell Y.

To focus on narrow correlations, we chose Δt = 1 ms; for medium correlations, Δt = 20 ms.

Modeling Propagating Bursts of Activity

Under some conditions, bursts of firing activity appeared to propagate across the retina in varying directions. We calculated the correlation function expected between two ganglion cell spike trains under a simple model for such bursts. Assume that a stripe of activity of width h travels at velocity v (Figure 9A). Outside the stripe, cells are silent, inside they fire at rate a. Consider two cells, X and Y, separated by a distance l along a line with angle ϑ relative to the stripe. The stripe will reach the two cells with relative delay

$$\tau(\vartheta) = \frac{l}{v}\sin\vartheta$$

For waves at this angle the cross-correlation function is

$R_w(t|\tau)$ = correlation function under waves of width h, velocity v, and relative delay τ

$$= \begin{cases} a\left(1-\frac{|t-\tau|}{h/v}\right), & \text{if } |t-\tau|<h/v \\ 0, & \text{else} \end{cases}$$

Assume that waves are equally likely to travel in all directions. Then the probability distribution of the relative delay, τ, is

$$p(\tau) = p(\vartheta)\frac{d\vartheta}{d\tau} = \begin{cases} \frac{1}{2\pi}\frac{v/l}{\sqrt{1-(v\tau/l)^2}}, & \text{if } |\tau|<l/v \\ 0, & \text{else} \end{cases}$$

Note that long delays near $\pm l/v$ are much more likely than short ones. Finally, the cross-correlation function averaged over many such waves becomes

$$R_w(t) = \int p(\tau)\cdot R_w(t|\tau)d\tau$$

Individual double-peaked cross-correlograms were then fitted with $b + R_w(t)$, using the measured intercellular distance, l. The baseline firing rate, b, the amplitude of the wave, a, its velocity, v, and width, h, were adjusted to produce the best fit.

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